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ARCHIVES OF OPHTHALMOLOGY

VOLUME 40 JULY 1948 NUMBER 1

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STUDIES IN EXPERIMENTAL OCULAR TUBERCULOSIS

XI. Effect of "Promin" and "Promizole" in Experimental Ocular Tuberculosis in the Normal Rabbit

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AND
EARL L. BURKY, M.D.
BALTIMORE

IN A PREVIOUS paper,[1] the effect of treatment with two sulfone compounds, "promin" (the sodium salt of p, p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate) and "promizole" (4,2-diaminophenyl-5′-thiazoylsulfone), on experimental ocular tuberculosis in the immune-allergic rabbit was reported. It was found that both these drugs exerted a strongly deterrent action on the course of the ocular tuberculosis. This deterrent action became evident after the third week of treatment. While histologic evidences of tuberculosis persisted in the healed eyes, the lesions were much fewer and less severe than in the control eyes. In transmission experiments, in which tissue from the eyes of treated rabbits was inoculated into normal rabbits, only one eye of the treated animals was found to be infectious.

These experiments were performed on immune-allergic rabbits—animals with a preexisting systemic tuberculosis at the time the eyes were inoculated. As a result of the systemic infection, these rabbits had a well developed acquired resistance, or immunity, to reinfection. It was not clear whether the deterrent action of the sulfone compounds noted in this experiment was due to a bactericidal action or to degradation or attenuation of the virulence of the organisms, thus allowing the resistance of the host to become more effective. The experiments here reported were undertaken with the idea of clarifying this point. The plan and execution of the experiments were identical with those previously reported, except that normal rabbits, in which no acquired immunity was present, were used as the experimental animals.

From the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital and University.

This work was supported in part by a grant from the John and Mary R. Markle Foundation.

1. Woods, A. C., and Burky, E. L.: Studies in Experimental Ocular Tuberculosis: X. Effect of "Promin" and "Promizole" on Experimental Ocular Tuberculosis in the Immune-Allergic Rabbit, Arch. Ophth. **39**:471 (April) 1948.

TECHNIC

Sixty normal rabbits, of mixed breed and sex, were inoculated on Dec. 13, 1946 in the anterior chamber of the left eye with 0.2 cc. of the paper filtrate of a six week old culture of a virulent strain of human tubercle bacilli. There was little or no reaction to the inoculation, and when the rabbits were examined one week later, on December 20, all eyes were recorded as showing no clinical activity. On December 27, evidence of ocular tuberculosis, consisting of small tubercles in the iris or in the cornea, with low grade pericorneal congestion, was present in all rabbits. The rabbits were then divided into three groups of the same number. The animals in group 1 were untreated and served as controls; those in group 2 were treated with "promin," and those in group 3, with "promizole." A suspension of the "promin" and "promizole" in water was sprayed over the pellets with which the rabbits were fed, so that a 1 per cent concentration of the drug was obtained in the food. A little "karo" syrup was added, and the pellets were dried. Each rabbit consumed about 1,000 Gm. of this mixture each week, or an approximate daily dose of 1.5 Gm. of "promin" or "promizole." Estimations of the concentration of the drugs in the blood were made by Dr. E. K. Marshall, of the department of pharmacology, on January 25, and again on April 15, at the close of the experiment. In these two estimates, the concentrations of "promin" were 0.2 and 4.4 mg. per hundred cubic centimeters, and those of "promizole," 0.5 and 2.4 mg. With the high dosage of the sulfone compounds, a greater concentration in the blood might properly have been expected. The only explanation for the relatively low figures consistently obtained is that the absorption of the drug from the gastrointestinal tract must have been low.

Treatment was begun on December 27. At the beginning of the experiment the average weight of the rabbits was as follows: group 1, 2,800 Gm.; group 2, 2,324 Gm., and group 3, 2,373 Gm. At the end of the experiment the average weights were as follows: group 1, 3,363 Gm.; group 2, 3,363 Gm., and group 3, 2,954 Gm. In short, all animals appeared to thrive on the diet. The rabbits were examined each week, and the degree of ocular tuberculosis was noted in the same manner as that described in the previous papers of this series. The average reading for each group was plotted each week on coordinate paper, so that a comparative graph of the course of the disease could be obtained.

By April 11, the disease in all three groups had pretty well run its course; the experiment was then terminated, the animals were killed and the eyes were removed. All ruptured eyes were sectioned for histologic study. The unruptured eyes in each group were used for transmission experiments.

OBSERVATIONS

Clinical Results.—The composite results are shown in figure 1. Treatment in groups 2 and 3 was started at the end of the second week. For two weeks thereafter there was no noticeable difference between the controls and the treated groups. At the end of the second week of treatment, the disease in the two treated groups became slightly less active than that in the control group, and this lessened activitiy in the treated groups was maintained throughout the course of the experiment, becoming more marked after the eighth week. The maximum difference was noted at the end of the eleventh week, when the control eyes showed an average

estimated clinical activity of 3.0 and the two treated groups an activity of 1.4. By this time, however, the greater number of the eyes had ruptured, and several animals had died of intercurrent infections. Thus, in the control group, at the end of the eleventh week, there were 19 survivors, and in 17 of these the inoculated eyes had become buphthalmic and had ruptured; in the group treated with "promin," all animals had survived, and the eyes of 17 had become buphthalmic and 13 had ruptured; in the group treated with "promizole," there were 17 survivors, and 14 eyes had ruptured. After rupture, a few of the eyes became phthisical; several others were secondarily infected, and in the remainder the corneas became so heavily vascularized that any accurate estimation of the degree of tuberculosis involvement was difficult or impossible. This course of ocular tuberculosis is the usual one in normal rabbits and is in sharp contrast with the course of the disease in the

Fig. 1.—Clinical results of treatment with "promin" and "promizole" in normal rabbit eyes. The ratings for the control group are indicated by the solid line; those for the rabbits treated with "promin," by the line of dashes, and those for the rabbits treated with "promizole," by the line of dots.

immune rabbit. In immune animals, rupture of the globe practically never occurs, and, except for isolated tubercles or infiltrates with local vascularization, the corneas remain clear. Therefore, after the eleventh week, in these normal rabbits there was little to be seen clinically except the vascular reaction and acute inflammation. This inflammation steadily decreased in all three groups; and at the conclusion of the experiment, at the seventeenth week, the average activity was estimated as 0.6 for the control group, 0.3 for the "promin"-treated group and 0.12 for the "promizole"-treated group. However, the eyes were so badly scarred and heavily vascularized that in the later stages of the experiment the evaluation of the severity of the disease was little more than an estimation of acute inflammatory reactions and the obvious damage done to the eyes. However, in summary, it may be stated that clinical examination of the eyes in the three groups showed that in general the inflammatory picture appeared less severe in the two treated groups and subsided earlier than in the untreated group.

Histologic Results.—At the conclusion of the experiment, 1 rabbit in the control group, none in the "promin"-treated group and 3 in the "promizole"-treated group had died of intercurrent infections. All the surviving rabbits, 19 in group 1, 20 in group 2 and 17 in group 3, were killed and the eyes enucleated. As before stated, the ruptured eyes

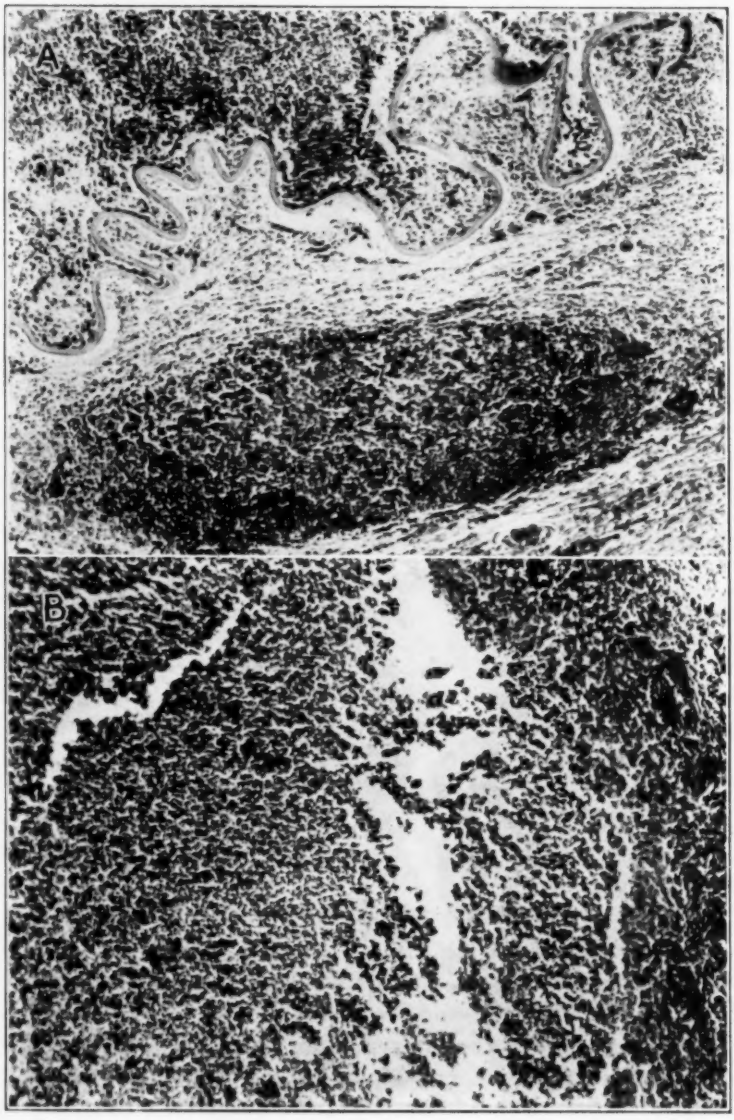

Fig. 2 (control eyes).—*A*, large tubercle of cornea, detachment of Descemet's membrane and tuberculous infiltration tissue in anterior chamber; *B*, tuberculous infiltration tissue in vitreous chamber. × 80.

(17 in group 1, 13 in group 2 and 14 in group 3) were sectioned for study, and the unruptured eyes were used for transmission experiments. The histologic pictures in the three groups were as follows:

GROUP 1 (Controls): With 1 exception, all the control eyes showed the picture of advanced, uncontrolled caseous tuberculosis, with large

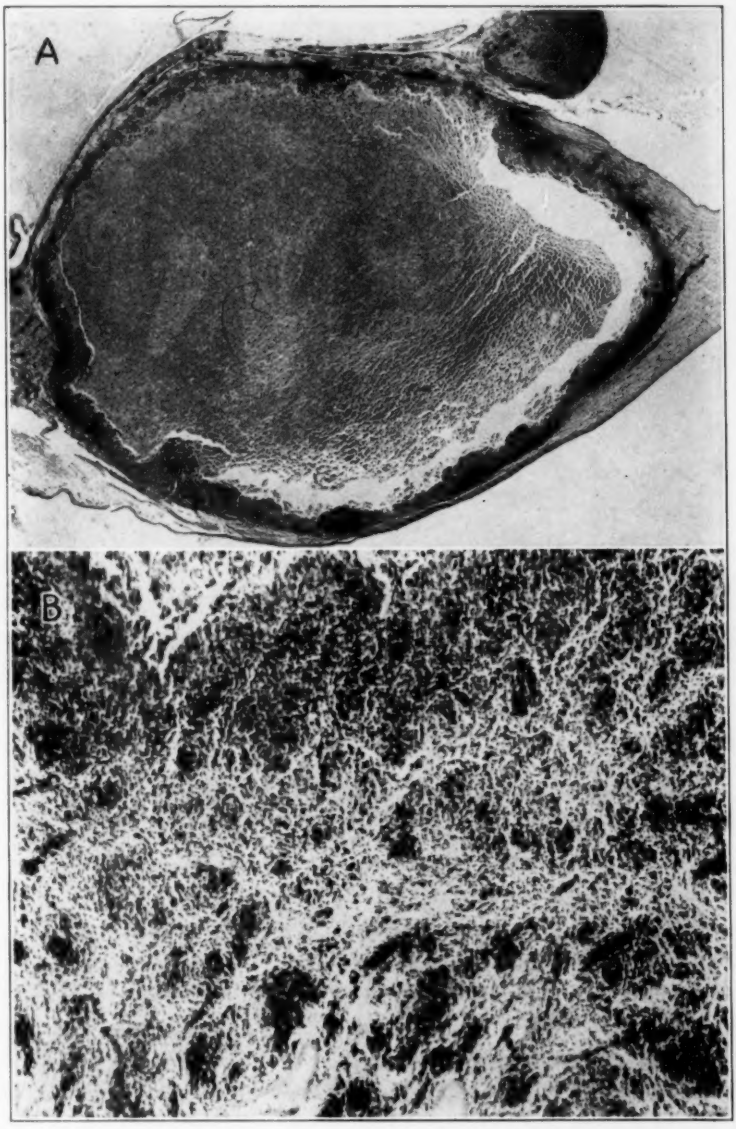

Fig. 3 (control eyes).—*A*, tuberculoma of ciliary body and necrosis of sclera; × 12. *B*, ciliary area in ruptured phthisical eye, showing active tuberculosis; × 80.

tubercles in the cornea, iris and ciliary body and with tuberculous infiltration tissue of epithelioid and giant cells invading both the anterior and the vitreous chamber. Figures 2 to 4 illustrate the typical pictures presented by this group. Figure 2*A* shows a tubercle of the cornea, with tuberculous infiltration tissue causing detachment of Descemet's membrane and invading the anterior chamber; figure 2*B*, tuberculous infiltration tissue invading the vitreous cavity; figure 3*A*, a buphthalmic eye with a large tuberculoma of the ciliary body invading the sclera; figure 3*B*, the ciliary area in a ruptured phthisical eye, almost filled with

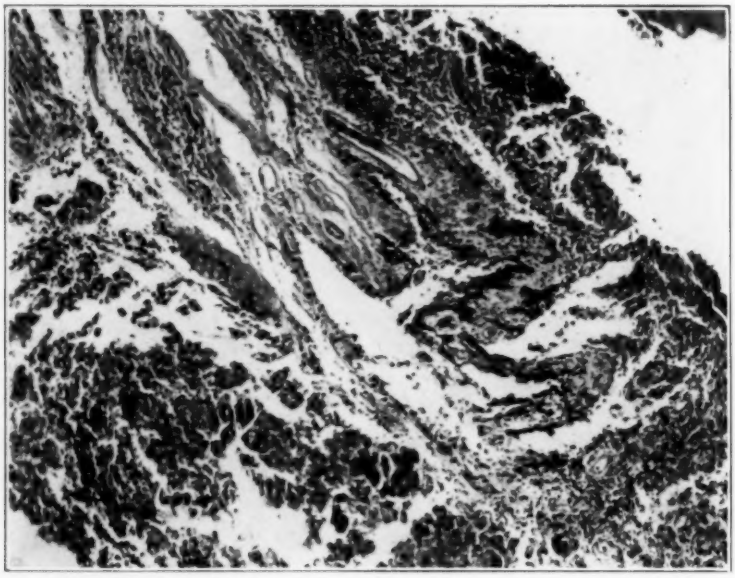

Fig. 4 (control eye).—Ciliary area in ruptured phthisical eye, showing activity subsiding and early fibrosis; × 80.

tuberculous tissue, and figure 4, a similar picture, but with the process somewhat burned out, with early fibrosis. The characteristic of all the eyes in this group was the spreading, unrestricted character of the tuberculous lesions and the tendency of tuberculous tissue, consisting chiefly of epithelioid and giant cells, to invade the cavities of the eye.

Group 2 (Eyes Treated with "Promin"): Practically all these eyes showed active tuberculosis, but in general the process was somewhat less active than that in the controls. Infiltration of the anterior and vitreous cavities was present in several eyes. Figure 5*A* shows the eye in which infiltration of the vitreous chamber was most prominent, but the infiltration was definitely less extensive than in the controls; figure 5 *B* shows a tuberculoma of the ciliary body with caseation and necrosis. Figure 6*A* shows a phthisical eye with generalized tuberculosis; but, again, the

process appeared less robust than in similar control eyes (fig. 3 *B*). Figure 6 *B* shows a phthisical eye in which the process was almost inactive, only small areas of activity being noted in the ciliary body.

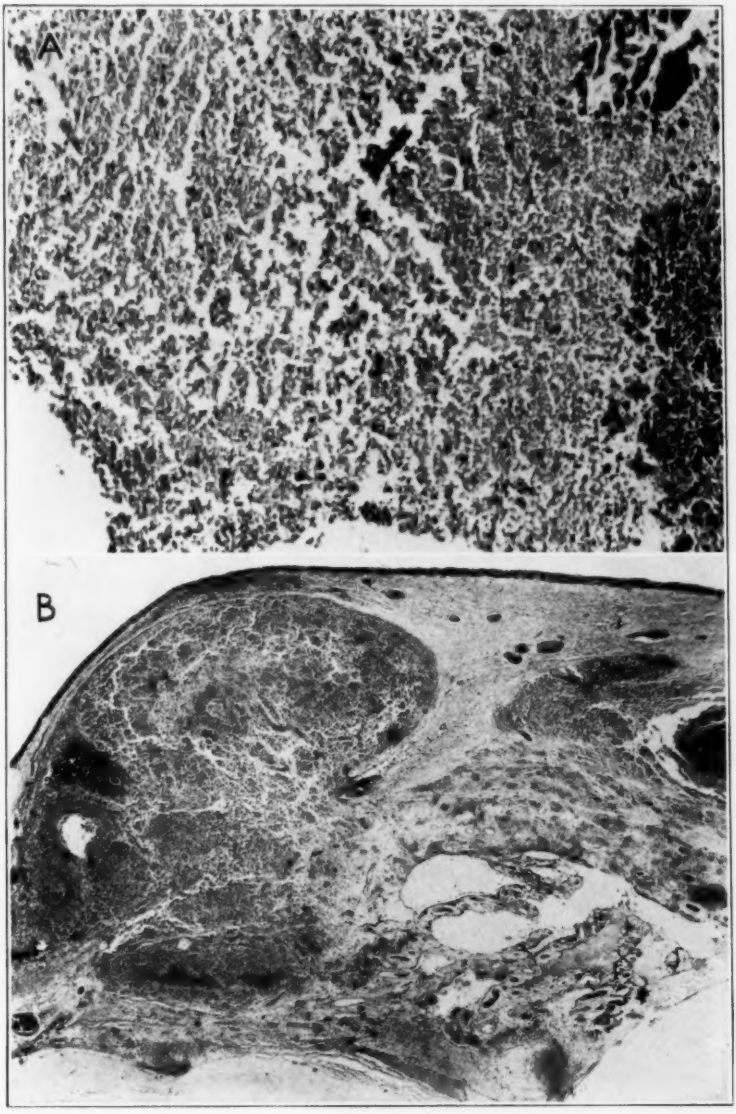

Fig. 5 (eyes treated with "promin").—*A*, tuberculous infiltration tissue in vitreous chamber; × 80. *B*, tuberculoma of ciliary body, with caseation and fibrosis; × 12.

On a numerical scale, the degree of tuberculous involvement in the eyes of this group of rabbits was rated as about 3, as compared with a rating of 4 given the control group.

Group 3 (Eyes Treated with "Promizole"): Again, in this group all the eyes showed pronounced active tuberculosis. If anything, the degree of activity in this group was slightly greater than in the rabbits

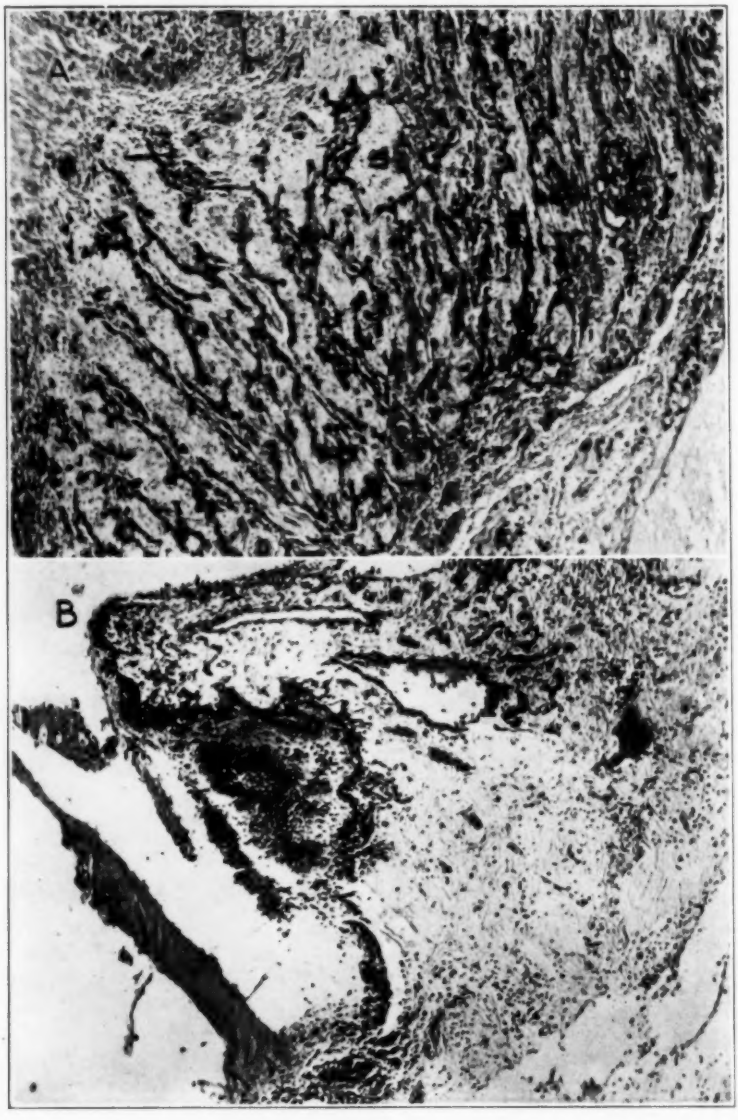

Fig. 6 (eyes treated with "promin").—*A*, ciliary area of phthisical eye, with early fibrosis; *B*, small areas only of activity in ciliary area. × 80.

treated with "promin," but, again, it appeared less than in the control group. On a numerical scale, 3+ would be a fair rating. Figure 7 *A* shows one of the eyes, with the most active process in this group, with

tuberculous infiltration tissue filling the anterior chamber. Figure 7 *B* shows another eye, with extreme activity, with tuberculosis tissue invading the vitreous. However, in this series, tuberculous infiltration of the

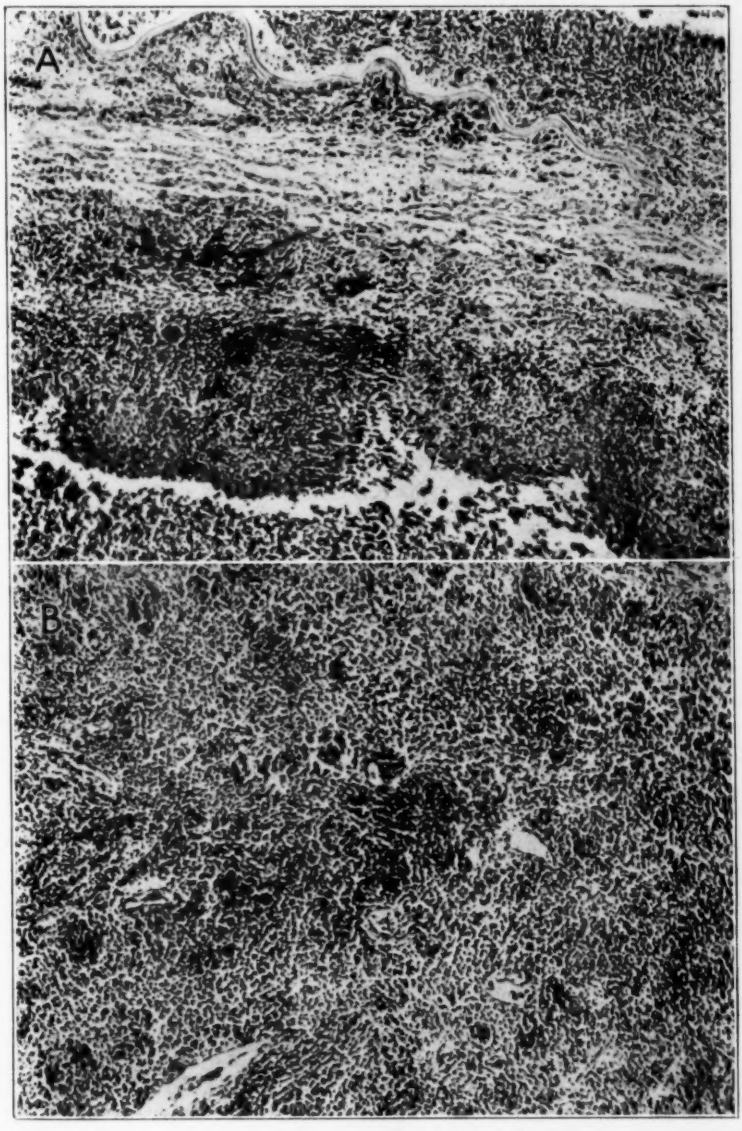

Fig. 7 (eyes treated with "promizole").—*A*, tuberculosis of cornea, with detachment of Descemet's membrane and tuberculous infiltration tissue in anterior chamber; *B*, tuberculous infiltration tissue in vitreous chamber. × 80.

vitreous was not so extreme as in the control group. Figure 8 *A* shows a fairly well circumscribed necrotic tubercle of the cornea, while figure 8 *B*

shows one of the better eyes, with the relatively clear cornea showing only minor tubercles and collections of leukocytes.

Transmission Experiments.—Two unruptured eyes in group 1, 7 unruptured eyes in group 2 and 3 unruptured eyes in group 3 were used

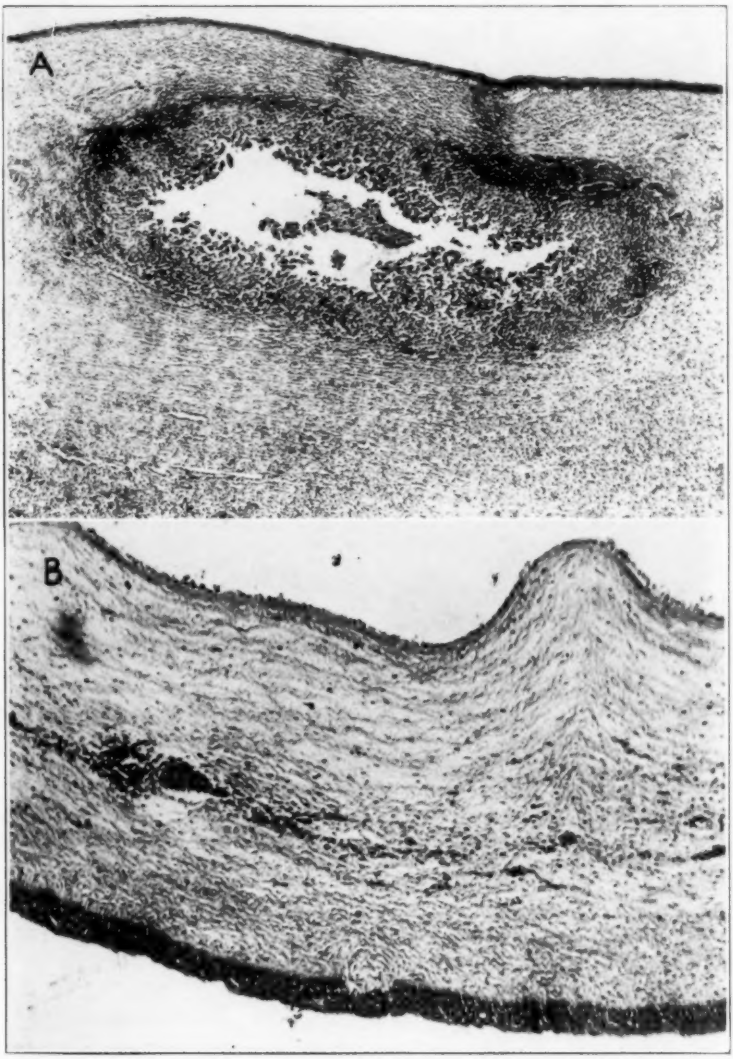

Fig. 8 (eyes treated with "promizole").—*A,* circumscribed, necrotic tubercle in cornea; × 40. *B,* trace of tuberculosis in cornea; × 80.

in transmission experiments, as before described. These eyes were opened under aseptic precautions, and the uveal tract was removed and ground up with sand in a sterile mortar with a little saline solution. The supernatant fluid was then inoculated into the anterior chamber of normal

rabbits. The rabbits were kept under observation for three months for the development of clinical ocular tuberculosis. They were then killed and the eyes sectioned. In every instance the normal eyes inoculated with

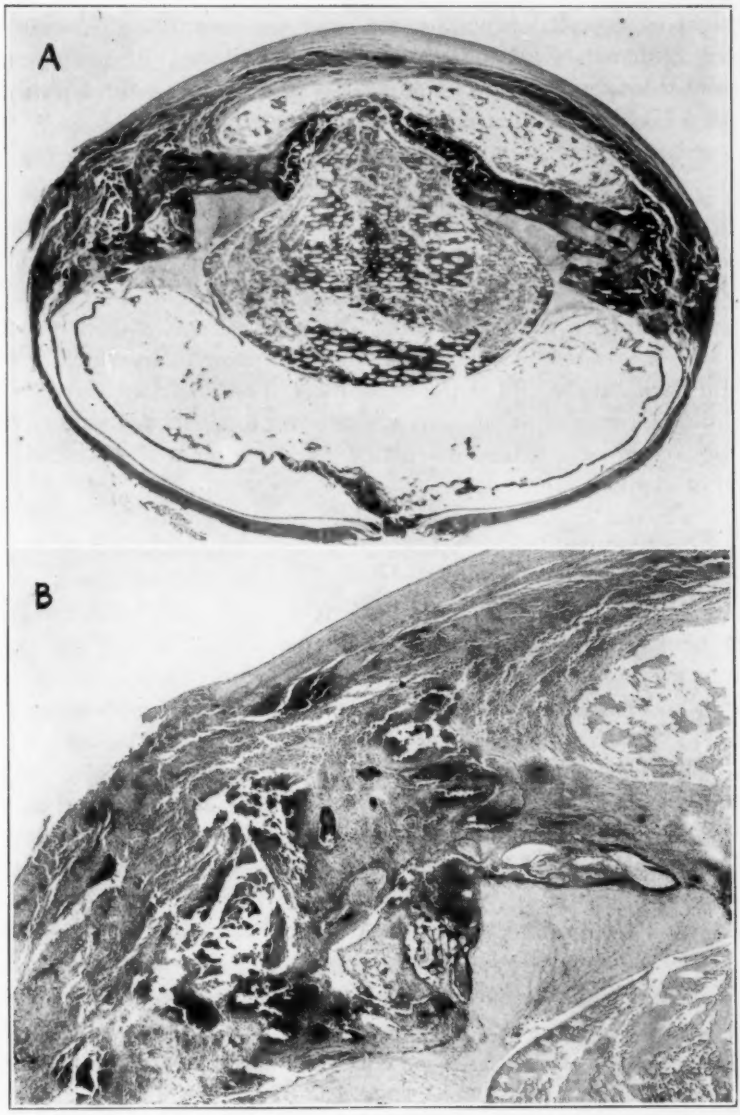

Fig. 9.—*A*, eye used in transmission experiments, showing advanced tuberculosis and invasion of anterior and posterior chambers; × 4½. *B*, ciliary region of same eye as that shown in *A*; × 12.

material from the eyes of these rabbits presented the typical clinical picture of ocular tuberculosis in the normal animal. The incubation period for each animal was roughly the same—eight to twelve days from the

time of inoculation to the onset of symptoms. The course of the disease was rapid in the secondarily inoculated rabbits, and the histologic picture was similar to that of the control group, as previously described, the eyes showing advanced, diffuse tuberculosis as the predominating lesion. As might be expected from the nature of the inoculation, several eyes showed evidence of secondary infection, manifested by a few small abscesses throughout the eye. Figure 9 (*A* and *B*) shows the typical picture in a rabbit used for transmission experiments.

COMMENT

It is apparent that any deterrent action exerted by the "promin" and "promizole" treatment in these normal rabbits was extremely slight. While it is true that both the clinical and the histologic lesions in the eyes of the treated rabbits were slightly less severe than in the control eyes, the difference was not striking. The diseased eyes of both the controls and the treated rabbits must have contained large numbers of virulent bacilli at the end of the experiment. This was manifested by the transmission experiment, in which extensive tuberculosis developed in the eyes of the secondarily inoculated rabbits after a short incubation period of eight to twelve days.

The obvious explanation of the difference in results in the normal and in the immune-allergic rabbits is that the tuberculous infection in the normal rabbits was so massive that it was beyond the power of the "promin" and "promizole" to control. It is noteworthy that the onset of the ocular tuberculosis in the eyes of the normal rabbits was rapid, the first symptoms appearing two weeks after inoculation, in contrast with an incubation period of six weeks for the immune-allergic animals. This difference was present despite the fact that the eyes of the immune-allergic rabbits received a much more massive inoculation.

While treatment was instituted in both groups at relatively the same time with respect to onset of symptoms, nevertheless, the ocular lesions developed with much greater rapidity in the normal rabbits; and after three weeks of treatment, at which time the first deterrent action was noted in the immune-allergic rabbits, the degree of clinical ocular tuberculosis in the normal rabbits was greater than in the immune-allergic series. Thus, if one accepts the indication of the first experiment, i.e., that three weeks' treatment with this dose is necessary before any deterrent action can be expected of these sulfone compounds, it is evident that as regards massiveness of infection alone a vastly greater therapeutic task was imposed in this experiment than in the previous experiment.

The simple facts are that in the presence of such a massive infection, in animals without systemic immunity, the "promin" and "promizole" exhibited only a slight deterrent action on the tuberculous process, whereas with a less extensive and a restrained infection, together with a well

developed systemic immunity, these sulfone compounds exhibited a strongly deterrent action on the ocular disease.

This observation does not give a clear answer to the original question, namely, whether the deterrent action of "promin" and "promizole" was due to a direct bactericidal action on the bacilli or to a depression and attenuation of their virulence, thus allowing the resistance of the host to become more effective. It is, however, strongly indicative. In the presence of massive infection, a slight deterrent action was still noticeable, while in the presence of a less intense and a restrained infection the deterrent action was pronounced. Thus, it would appear that "promin" and "promizole" exert, by one means or another, a limited bactericidal action against the Mycobacterium tuberculosis. When the dissemination and propagation of the bacilli are restrained by a systemic immunity, this bactericidal action is clearly evident; when the dissemination and growth of the bacilli are unrestrained, there results an infection so massive that it is beyond the therapeutic range of the sulfone drugs. It must be granted that an almost equally good case can be made for the second alternative, i.e., that these sulfone compounds depress the growth and virulence of the organisms, thus allowing the systemic immunity to become more effective. However, when one considers the over-all picture, notably, the observation that the deterrent action of these sulfone compounds was pronounced only when the growth and dissemination of the organisms was first restrained by the systemic immunity, it appears more logical to conclude that the deterrent action is due to a limited bactericidal effect.

CONCLUSIONS

"Promin" and "promizole," used in the same dose as that which had a pronounced deterrent effect on ocular tuberculosis in the immune-allergic rabbit, produced only a slight deterrent action on ocular tuberculosis in the normal animal. This slight action was first noticed clinically after two weeks of treatment and was somewhat more pronounced after eight weeks of treatment. There was, however, only a slight difference in the degree and extent of the disease when the eyes of the control and those of the treated animals were examined histologically. All transmission experiments with the treated animals gave positive results, indicating that large numbers of living virulent bacilli were still present in the eyes.

An examination of the results of this experiment, and of the similar experiment with immune-allergic rabbits, indicates that "promin" and "promizole" probably have a limited bactericidal effect on the tubercle bacillus, this action becoming clearly evident only when the tuberculous process is so restrained by a systemic immunity that it is brought within the therapeutic range of these sulfone compounds.

Wilmer Ophthalmological Institute.

GRANULAR CELL MYOBLASTOMA OF THE ORBIT

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WITHIN recent years much has been written by the pathologists about a type of tumor variously designated by the names "myoblastic myoma," "myoblastoma," "rhabdomyoma" and "granular cell myoblastoma." Confusion still exists as to the correct terminology, but all are agreed on the pathologic picture of this tumor type. Using the name myoblastoma (*Myoblastenmyom*), Abrikossoff,[1] in 1926, first described this peculiar tumor of striated muscle tissue. The characteristic microscopic features may be summarized as follows: (1) large polyhedral cells, 20 to 60 microns in diameter, constitute a nodular accumulation of neoplastic cells; (2) the cytoplasm stains only faintly with eosin and contains many coarse neutrophilic granules; (3) cross or longitudinal striations are rarely seen; (4) the nuclei are small and never show the irregularity associated with malignancy; (5) the tumor cells, individually or in groups, are surrounded by a thin network of connective tissue fibers; (6) the cells are devoid of fat. Later, in 1931, he[2] described the histologic features of four different varieties of this tumor. Ravich, Stout and Ravich[3] differentiated these types in the following manner:

(1) The typical form made up of round, egg-shaped, or elongated myoblasts from 20 to 25 microns long with granules but without longitudinal or cross striations; (2) a variation of the first type in which some cells show longitudinal or cross striations; (3) a hypertrophic form with cells from 40 to 60 microns and sometimes multinucleated. These first three groups are all composed of granular cells and all are benign tumors; (4) malignant myoblastic myoma in which the

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Read before the Eighty-Third Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., June 6, 1947.

From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology of the Presbyterian Hospital of New York.

1. Abrikossoff, A.: Ueber Myome ausgehend von der quergestreiften willkürlichen Muskulatur, Virchows Arch. f. path. Anat. **260**:215-233, 1926.

2. Abrikossoff, A. I.: Weitere Untersuchungen über Myoblastenmyome, Virchows Arch. f. path. Anat. **280**:723-740, 1931.

3. Ravich, A.; Stout, A. P., and Ravich, R. A.: Malignant Granular Cell Myoblastoma Involving the Urinary Bladder, Ann. Surg. **121**:361-372 (March) 1945.

myoblasts are not granular, but assume atypical aspects and vary in size so that the tumor resembles a polymorphous sarcoma.

It is the fourth type which has led to the greatest amount of confusion. Most malignant tumors termed myoblastomas belong either to the rhabdomyosarcoma group or to the fourth subdisivion of Abrikossoff. The cells of the latter type do not have a granular cytoplasm and rarely show the cross striations so characteristic of rhabdomyosarcoma.

Differentiation between granular cell myoblastoma and rhabdomyoma is not always easy; but, as pointed out by Cappell and Montgomery,[4] the relative absence of cross and longitudinal striations and the primitive nature of the myoblasts are diagnostic of granular cell myoblastoma. However, as emphasized by Stout,[5] the demonstration of cross striations in rhabdomyosarcoma is often a painstaking task, which will be successful only if the tumor material is well fixed and stained properly. Stout uses either Masson's trichrome stain, containing acid fuchsin; Heidenhain's hematoxylin stain or, if Zenker's solution is used for fixation, the phosphotungstic acid hematoxylin stain. Furthermore, he expressed the belief that high magnification is essential for the detection of these striations. This author expressed agreement with Howe and Warren[6] that myoblastomas should be separated from the rhabdomyosarcomas. Cappell and Montgomery,[4] on the other hand, stated that there is no absolute line of demarcation between these two growths and that transitions undoubtedly occur, which lead to difficulty in classification. A careful review of the recent literature convinces me that no uniformity in terminology exists at present, but that the two growths do present certain differences, not only in cellular structure but in clinical behavior. The rhabdomyoma is an infiltrative growth, always malignant or potentially so, while the granular cell myoblastoma is often encapsulated and is usually benign. The explanation offered by Cappell and Montgomery[4] for this apparent paradox, i.e., that myoblastoma, with its primitive character, is the more benign growth, lies in the presence or absence of any anaplastic or primitive round and short spindle cells in the primary growth. In myoblastoma the cellular structure is more homogeneous and uniform, and groups of highly anaplastic cells are absent. According to Ewing,[7] "a notable feature [in myoblastoma] is the tendency of the overlying skin to develop epidermoid carcinoma, which has sometimes proved malignant." Neither

4. Cappell, D. F., and Montgomery, G. L.: On Rhabdomyoma and Myoblastoma, J. Path. & Bact. **44**:517-548 (May) 1937.

5. Stout, A. P.: Rhabdomyosarcoma of the Skeletal Muscles, Ann. Surg. **123**: 447-472 (March) 1946.

6. Howe, C. W., and Warren, S.: Myoblastoma, Surgery **16**:319-347 (Sept.) 1944.

7. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 4, Philadelphia, W. B. Saunders Company, p. 248.

of these growths presents any characteristic clinical appearance, and the differentiation is purely a histologic one. Xanthoma is another tumor with which this growth has been confused, but the absence of fat in the cells and the granular character of the cytoplasm in myoblastoma are the differentiating features.

The histogenesis of myoblastoma is much discussed in the literature, and there are two schools of thought with respect to its origin. It is believed by some to be a true neoplasm of immature, proliferating skeletal muscle cells (myoblasts) and by others to be a degenerative lesion, the cells being muscle fibers undergoing necrobiotic changes. Abrikossoff[1] first concluded that the tumors resulted from such a degenerative process following trauma or inflammation in striated muscle, but he later stated the belief that some of the tumors arise from primitive myoblasts, representing embryonic rests. The fact that myoblastomas most commonly arise from the muscular tissue of the tongue is strong support for the muscular origin of these growths, but they do occur in locations normally devoid of striated muscle tissue. For example, they have been reported in the gum of the newborn infant—a region devoid of muscle tissue of any sort. Their occurrence in such locations certainly bespeaks the dysontogenetic origin of some of these growths. Therefore, in view of the present inadequate knowledge, it would seem fair to say that some myoblastomas do arise from embryonic rests whereas others probably result from degenerative changes occurring in striated muscle tissue.

Myoblastic tumors are moderately common, and their distribution is widespread. According to the report of Crane and Tremblay,[8] of 162 such tumors, 37.6 per cent occurred in the tongue, and 20.4 per cent in the skin and subcutaneous tissue, while less frequently they were found in muscle and in the maxilla, breast, larynx, vocal cords, mandible, lip, trachea, bronchus, ear and alveolar process. Involvement of the orbit by such a new growth has rarely been observed. While the literature contains several references to granular cell myoblastoma having been found in the orbit, a critical analysis of these cases casts doubt on the accuracy of the diagnosis in some of them. For example, the first case reported in 1935 by Sjögren,[9] under the title "Myoblastoma Malignum Orbitae," is excluded. Here was described in detail the case of an 8 year old boy in which the clinical course, as well as the pathologic descriptions, was typical of rhabdomyosarcoma. The reports of Mitvalsky[10] and of Pieck[11]

8. Crane, A. R., and Tremblay, R. G.: Myoblastoma (Granular Cell Myoblastoma or Myoblastic Myoma), Am. J. Path. **21**:357-375 (March) 1945.

9. Sjögren, H.: Myoblastoma malignum orbitae, Arch. f. Ophth. **134**:333-340, 1935.

10. Mitvalsky: Eine Ciliarkörpergeschwulst nebst Bemerkungen, Arch f. Augenh. **28**:152-165, 1893-1894.

11. Pieck, C. F. M.: A So-Called Myoma of the Ciliary Body, Ophthalmologica **99**:471-475 (May) 1940.

of myoblastoma of the ciliary body are also to be questioned because the smooth muscle origin of the tumors would now classify them as leiomyomas. The first authentic case of orbital myoblastoma is that of von Bahr,[12] who observed this growth in the region of the lacrimal sac. The patient had had lacrimation for several years, with the development of a mass in the region of the lacrimal sac three weeks previously. At her first visit acute dacryocystitis with perforation was observed; this inflammation promptly subsided, leaving a firm tumor the size of a large pea. Extirpation of this growth was easily accomplished, without subsequent recurrence. Histologically the tumor consisted of bundles of large cells, 40 to 50 microns in length, with granular cytoplasm, large ovar nuclei and no cross striations. At the periphery of the lesion the cells were larger and thicker with a yellower protoplasm and larger nuclei, resembling transitional forms of true muscle cells. Powell,[13] in reporting a case of primary granular cell myoblastoma of the ovary, referred to the presence of a metastatic nodule in the eyelid. In a recent article on myoblastoma of the eyelid, Cristini,[14] after recording a case of his own, referred to 5 previously reported cases. A careful study of the photomicrographs and pathologic descriptions of these tumors leaves one in a quandary as to their proper classification. It is possible that some belong to the rhabdomyoma group, since the presence of cross striations is frequently mentioned. If, however, one accepts these 6 cases as instances of granular cell myoblastoma, together with the case of von Bahr[12] and that of Powell,[13] the 2 cases here reported are the ninth and tenth on record. Since these tumors occur in such diffuse locations in the body, it is surprising that more of them have not been found in the orbit. With the hope, therefore, of focusing the attention of ophthalmic pathologists on tumors of this type, the present 2 cases are recorded.

REPORT OF CASES

CASE 1.—R. H., a white woman aged 36, was first seen Feb. 19, 1946. She gave a history of drooping of the right upper lid of nineteen months' duration, with proptosis first becoming evident ten months later. The condition progressed at first but had recently remained stationary. There were no inflammatory signs or discomfort except that produced by the ptosis. Examination revealed vision of 20/20 in each eye, 5 mm. of ptosis of the right upper lid and 6 mm. of exophthalmos of the right eye. The upward movements of this eye were seriously impaired. A firm, movable mass was palpable just under the upper orbital margin. A roentgeno-

12. von Bahr, G.: A Case of Myoblastic Myoma of the Lacrimal Sac, Acta ophth. **16**:109-115, 1938.

13. Powell, E. B.: Granular Cell Myoblastoma, Arch. Path. **42**:517-524 (Nov.) 1946.

14. Cristini, G.: "Mioblastoma della palpebra" (studio anatomo-clinico), Rassegna ital.d'ottal. **15**:207-223 (May-June) 1946.

gram of the orbit showed increased density of the soft tissues but no other changes. On February 26 a well encapsulated tumor, measuring 8 by 4 by 3 mm., was removed from the orbit by blunt dissection. The growth was in contact with the levator muscle but did not appear to arise from that muscle. Convalescence was

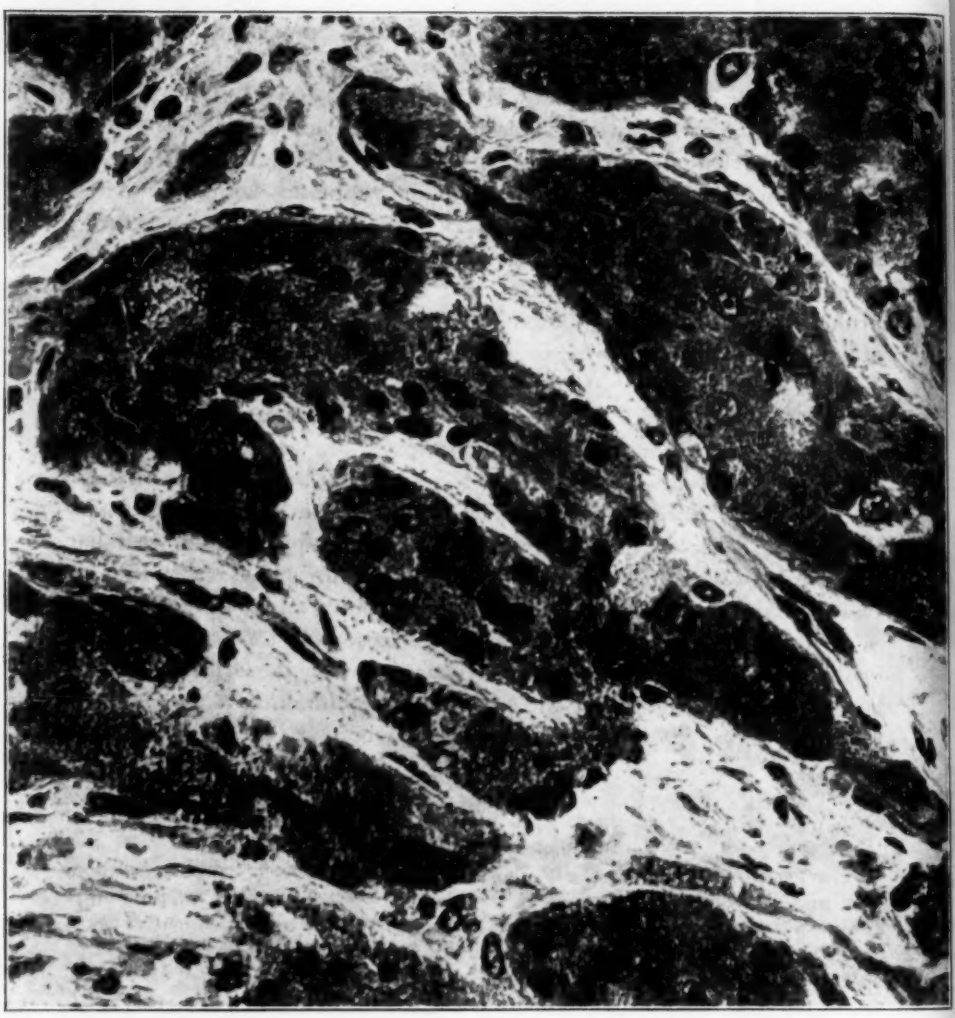

Fig. 1 (case 1).—Cords of tumor cells interspersed between connective tissue stroma. The cells show a large amount of granular cytoplasm. Trichrome stain; magnification, 500.

uneventful except that the ptosis became complete. On July 24, resection of 20 mm. of the levator muscle was performed. This resulted in an incomplete, but relatively satisfactory, correction of the ptosis. At the time of this operation no gross evidence of recurrence could be detected in the orbit, nor did the excised

portion of the levator muscle reveal any microscopic evidence of a new growth. The patient shortly thereafter returned to her home in Greece, so that no direct follow-up observation has been possible; judging from recent letters, however, she is still free from recurrence.

Fig. 2 (case 1).—Higher magnification (× 1,000) of a portion of figure 1.

The pathologic report on the tumor, as submitted by Dr. A. Purdy Stout, follows: "Microscopically the tumor was composed of differentiated granular myoblasts. They were arranged in cords, and the individual cells were rather large, with exquisitely and strikingly acidophilic granules in the abundant cytoplasm

surrounding the small, inactive nucleus. The growth was sharply circumscribed, but there appeared to be tumor cells in the fibrous sheath surrounding it, so that it was impossible to know whether or not the entire growth had been removed. Its appearance indicated that the growth was benign" (figs. 1 and 2).

CASE 2.—W. C., a white man aged 40, was first seen on April 2, 1945, with a nonpainful lump at the nasal end of the left lower lid of one month's duration. Vision was unaffected, and his only complaint was the increasing swelling and redness of the lid. Examination revealed a tense, red, indurated swelling, about 2 by 3 cm., occupying the nasal two thirds of the left lower lid. The conjunctiva in the lower fornix was chemotic, and the mass had displaced the globe upward and temporally (fig. 3). Roentgenograms of the orbit showed only a localized area of increased density of soft tissues in the lower nasal aspect of the left orbit. Biopsy of the orbital mass was made because the infiltrative nature of the neoplasm

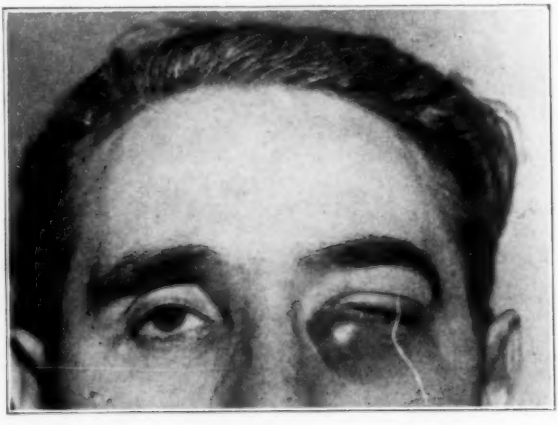

Fig. 3 (case 2).—Appearance of patient at the time of the initial examination.

rendered complete excision impossible. Nine days later, after the diagnosis of granular cell myoblastoma had been established, exenteration of the orbit was performed. This was followed by recurrence of a nodule along the lower orbital margin, for which radical excision, with skin grafting, was performed on June 26. The wounds healed, and the patient remained free from clinical evidence of recurrence unitl Sept. 12, 1945, when he returned, complaining of the rather rapid development of a lump at the angle of the jaw. A large, firm mass was present in the region of the submaxillary gland. The growth rapidly enlarged until Nov. 20, 1945, when a radical dissection of the structures in the submental and submaxillary triangles was done by Dr. John M. Hanford. Histologic examination showed the lymph nodes to be largely replaced with tumor tissue identical in character with the primary growth in the orbit. Another mass appeared in the left cheek within six weeks. This growth was thought to be inoperable; so roentgen therapy was given, with considerable regression in size of the nodules. Recurrences have since taken place, and the growth is invading the bones of the orbit and face. The patient, when last seen on May 29, 1947, showed signs of generalized metastasis.

The pathologic report, as submitted by Dr. A. Purdy Stout, follows: "Sections of the biopsy specimen from the original tumor were stained with hematoxylin and eosin and by Masson's trichrome method. They showed a tumor that was made up of masses of rounded and polygonal cells, of relatively large size and moderately well demarcated borders, although in many instances these were so ill defined that the cells appeared to coalesce. The characteristic of the cytoplasm was the presence of a large number of fine, moderately acidophilic granules. The

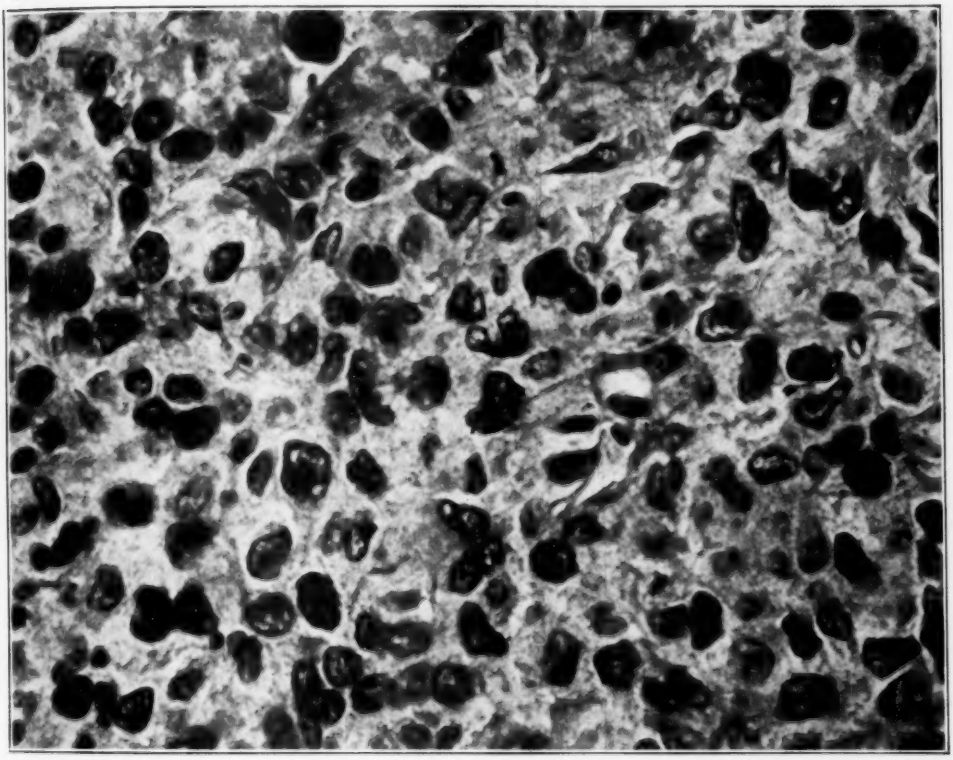

Fig. 4 (case 2).—Myoblastic cells, which are less embryonic than those in case 1. The cytoplasm is less granular and there is a tendency toward ribbon cells, but without striations. Hematoxylin and eosin stain; magnification, × 750.

nuclei were moderately large and hyperchromatic and showed occasional mitoses. The cells had the characteristics of a malignant form of granular cell myoblastoma. Nowhere was the arrangement characteristic of the benign form (fig. 4).

"The mass in the orbit was large, measuring 29 by 28 mm. on the slide. The tumor pressed on the conjunctival sac, invaded one of the lids and was microscopically, although not grossly, invasive. The morphologic character both of the main tumor and of the recurrent nodule, removed after exenteration of the orbit, remained unchanged and was the same as that of the metastatic tumor in the lymph node.

"The diagnosis was that of granular cell myoblastoma of the orbit."

SUMMARY

Granular cell myoblastoma is a relatively common tumor and widely distributed throughout the body. Since its occurrence in the orbit is rare, 2 cases are reported. The tumors in these cases presented no characteristic clinical picture, and the differential diagnosis was purely a histologic one. The tumor is more commonly benign, but in 1 of the present 2 cases it was malignant.

635 West One Hundred and Sixty-Fifth Street.

EXPERIMENTAL INVESTIGATION OF THE PATHOGENICITY OF DIPHTHEROIDS ISOLATED FROM THE HUMAN CONJUNCTIVA

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GENERAL CONSIDERATIONS

Bacteriologic Features of Diphtheroids.—The first attempt to establish an etiologic relation between a diphtheroid and a disease of the eye dates back to 1879, when Italian investigators[1] isolated Corynebacterium xerose during the course of an institutional epidemic of xerophthalmia. Later, in 1883, German workers demonstrated the presence of diphtheroids on the conjuctiva of patients with a nutritional deficiency. However, it was soon realized that these bacteria are usually present on normal and inflamed conjunctivas, as well as on other normal and diseased surfaces of the body. It is of interest to note that in a recent review of the subject, published by the British Medical Research Council, the statement was made[2]:

> It is very doubtful if *C. xerose* is even now sufficiently well characterized to deserve a specific rank. So authors present a picture formed from composite conceptions of various workers.

Likewise, the report of the Pickett-Thomson Research Laboratories[3]

This study was aided by a grant from the Columbia Foundation.

Read at a meeting of the Society of American Bacteriologists, Philadelphia, May 13, 1947.

From the Laboratory for Ophthalmic Research, Mount Zion Hospital, San Francisco; the Department of Pathology, University of California School of Medicine, and the Laboratories of the Jewish Hospital, Philadelphia.

1. Andrews, F. W., and others: Diphtheria, Medical Research Council, London, His Majesty's Stationery Office, 1923, chap. 11, p. 370.

2. Hewlett, R. T., and Bulloch, W.: A System of Bacteriology in Relation to Medicine, Medical Research Council, no. 5, London, His Majesty's Stationery Office, 1930, chap. 3, p. 133.

3. Thomson, D., and Thomson, R.: The Classification and Identification of Certain Chromogenic Bacteria by Microphotography, Ann. Pickett-Thomson Research Lab. **2**:51, 1925.

emphasized that the systematic study of the diphtheroids is still in a state of confusion, owing to the extreme variability in the morphologic and biochemical characteristics of these organisms.

In general, corynebacteria are described as nonmotile, gram-positive, aerobic, nonsporulating rods, resembling Corynebacterium diphtheriae, usually showing uneven staining and variable morphologic changes during growth. Young cultures (eight to twelve hours old) show solid forms only, but as they get older (twenty-four to forty-eight hours) the bacilli acquire elongated, pear-shaped forms, clubbing and barring. The fermentation of carbohydrates is variable.[4] Agglutination tests are difficult to perform because of spontaneous clumping. Identification by other serologic methods is likewise unsatisfactory, since complete studies have not been made of their antigenic structure.

The ophthalmologist who performs an iridectomy or an operation for cataract is interested to know whether or not diphtheroids, which are almost constantly present on the normal and inflamed conjunctiva, may exert serious injury when transferred by means of a surgical instrument to the interior of the eye. Axenfeld and his students[5] answered this question negatively over a generation ago. Nevertheless, it was deemed important to reinvestigate this problem in the light of the following new developments:

1. Many species of diphtheroids are now recognized as capable of producing disease.[6] Thus, a fatal human case of meningitis[7] and another of endocarditis[8] have been ascribed to corynebacteria. Likewise, cutaneous lesions in service men who had returned from the New Hebrides and the Mariana Islands of the Pacific were recently reported to be due to Corynebacterium hemolyticum.[9] With newer methods, specific toxins have been

4. Barratt, M. M.: A Study of Corynebacterium Diphtheriae and Other Members of the Genus Corynebacterium with Special Reference to Fermentative Activity, J. Hyg. **23**:241, 1924.

5. Axenfeld, T.: Bacteriology of the Eye, translated by A. MacNab, New York, William Wood & Company, 1908, pp. 196-198.

6. Bruce, E. A.: Ophthalmia in Sheep Caused by Corynebacterium Enzymicum and Its Transmission to Man, Canad. J. Comp. Med. **7**:369, 1943. Cotchin, E.: Corynebacterium Equi in the Submaxillary Lymph Nodes of Swine, J. Comp. Path. & Therap. **53**:298, 1943. Merchant, I. A.: A Study of the Corynebacteria Associated with Diseases of Domestic Animals, J. Bact. **30**:95, 1935. Fraser, I. C.; Robson, J. M., and Scott, A. A. B.: Experimental Diphtheroid Infections of the Rabbit's Eye and Their Treatment, Brit. J. Pharmacol. **1**:241, 1946.

7. Tesdal, M.: Fatal Meningitis Caused by a Corynebacterium, Acta med. Scandinav. **83**:351, 1934.

8. Foord, A. G., and Stone, W. J.: Endocarditis Caused by Diphtheroid Bacillus, Am. J. Clin. Path. **4**:492, 1934.

9. MacLean, P. D.; Liebow, A. A., and Rosenberg, A. A.: A Hemolytic Corynebacterium Resembling Corynebacterium Ovis and Corynebacterium Pyogenes in Man, J. Infect. Dis. **79**:69, 1946.

demonstrated for Corynebacterium pyogenes,[10] the cause of abscesses in cattle and swine, and for Corynebacterium ovis,[11] which produces caseous and suppurative adenitis and pulmonary abscess in sheep and ulcerative lymphangitis in horses.

2. A number of micro-organisms, ordinarily nonpathogenic for animals, may acquire pathogenicity, while others become more virulent when inoculated in a medium of mucin.

We therefore undertook to demonstrate whether or not diphtheroids are pathogenic in special circumstances, as in the presence of mucin, and whether they can produce a soluble toxin.

Properties of Mucin.—Mucin, which is manufactured in the glands of the conjunctiva and other mucous membranes, is a protein conjugated with carbohydrate. Like gastric mucin, it contains, presumably, mucoitin-sulfuric acid.[12] When mucin is used as a vehicle in which to suspend certain bacteria, the organisms may acquire an increase in virulence for experimental animals. The mechanism is essentially as follows: Mucin functions as a protective capsule for the micro-organisms, permitting them to proliferate and survive in vivo. It also decreases phagocytosis and intracellular digestion of bacteria and reduces the bacteriolytic power of serums.[13] Thus far, this phenomenon has been demonstrated, among others, for meningococci,[14] pneumococci,[13c] typhoid bacilli,[13f] Hemoph-

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10. Lovell, R.: Studies on Corynebacterium Pyogenes with Special Reference to Toxin Production, J. Path. & Bact. **45**:339, 1937.

11. Petrie, G. F., and McClean, D.: The Inter-Relations of Corynebacterium Ovis, Corynebacterium Diphtheriae and Certain Diphtheroid Strains Derived from the Humas Nasopharynx, J. Path. & Bact. **39**:635, 1934.

12. Levene, P. A.: Hexosamines and Muco-Proteins, Monographs on Biochemistry, London, Longmans, Green & Co., 1925.

13. (*a*) McLeod, C.: The Mode of Action of Mucin in Experimental Meningococcus Infection, Am. J. Hyg. **34**:51, 1941. (*b*) Nungester, W. J., and Klepser, R. G.: A Possible Mechanism of Lowered Resistance to Pneumonia, J. Bact. **35**:32, 1938. (*c*) Nungester, W. J.; Jourdonais, L. F., and Wolf, A. A.: Effect of Mucin on Infections by Bacteria, J. Infect. Dis. **59**:11, 1936. (*d*) Tunnicliff, R.: Action of Gastric and Salivary Mucin on Phagocytosis, ibid. **66**:189, 1940. (*e*) Anderson, C. G., and Oag, R. K.: The Effect of Gastric Mucin on the Pathogenicity of the Meningococcus and Other Organisms, Brit. J. Exper. Path. **20**:25, 1939. (*f*) Rake, A.: Enhancement of Pathogenicity of Human Typhoid Organisms by Mucin, Proc. Soc. Exper. Biol. & Med. **32**:1523, 1935. (*g*) Mishulow, L.; Klein, I. F.; Liss, M. M., and Leifer, L.: Protection of Mice Against H. Pertussis by Serum, J. Immunol. **37**:17, 1939. (*h*) Griffitts, J. J.: The Use of Mucin in Experimental Infections of Mice with Vibrio Cholerae, Pub. Health Rep. **57**:707, 1942. (*i*) Olitski, L.: Mucin as a Resistance Lowering Substance, Bact. Rev. **12**:149, 1948.

14. McLeod.[13a] Nungester and Klepser.[13b] Nungester and others.[13c] Tunnicliff.[13d] Anderson and Oag.[13e]

ilus pertussis,[13g] Vibrio cholerae[13h] and the virus of influenza.[15] Since mucus (containing mucin) is increased in amount during the course of conjunctivitis when diphtheroids also increase in number, it seemed worth while to investigate the effects of mucin on diphtheroids which had been isolated from the human conjunctiva.

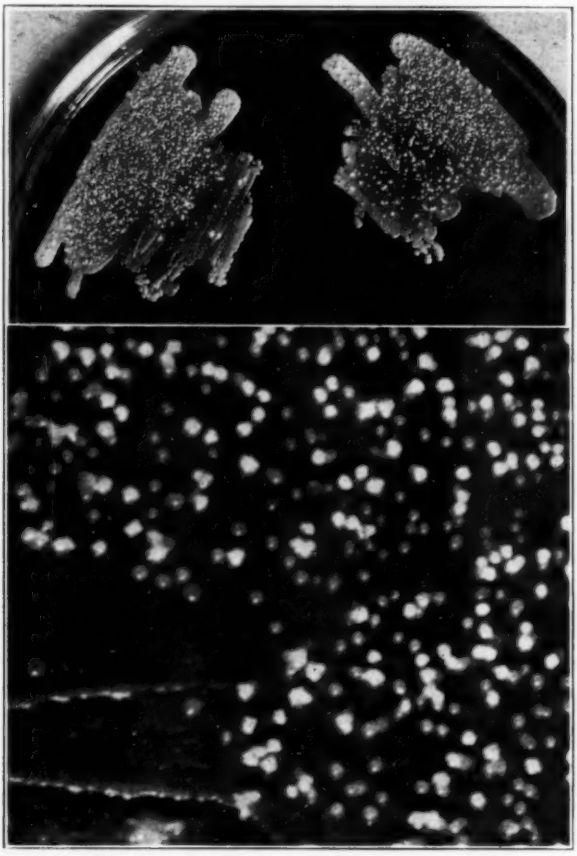

Fig. 1.—Dissociation in cultures of diphtheroids. Background shows original growth; surface colonies are mucoid variants (shown magnified in lower portion).

METHODS OF INVESTIGATION

Cultural Studies.—The cultures employed were isolated from normal human conjunctivas on plates of proteose 3 agar containing rabbit blood. The colonies when first appearing were minute, resembling dew drops. When forty-eight hours old they were small and transparent, with a

15. Wheeler, A. H., and Nungester, W. J.: Effect of Mucin on Influenza Virus Infection in Hamsters, Science **96**:2482, 1942.

slight opacity in the center. Fermentation of dextrose and levulose was usually observed after seven days. Sucrose, maltose and galactose were not hydrolyzed. Dissociation (variation), as might be expected, was noted when the medium was changed to one containing dextrose. The colonies now appeared larger, more opaque, creamy and mucoid (fig. 1). Gram-positive rods were present, as usual; but coccoid forms were also seen. These variants attacked dextrose, maltose and levulose slowly (twenty-one days). Pigmented (orange-yellow) colonies were also observed.[16] These bacteria did not ferment any of the carbohydrates here listed. By careful selection of smooth colonies, we attempted to maintain the stability of the strain used in the experimental studies.

In addition to the usual V, Y, and club forms, the variants often showed in Gram preparations coccobacillary rods, which resembled chains of streptococci. At first suspected of being contaminants, they were repeatedly replated and studied by means of dark field illumination and in hanging drop preparations, where they were recognized as tiny coccobacilli.

Technic of Inoculation.—After a demonstration by Dr. Michael Hogan, of the department of ophthalmology, University of California, we performed several preliminary experiments in order to acquire skill in the technic of injection into the anterior chamber of albino rabbit eyes without injuring the iris.[17] The animals were anesthetized by an intravenous injection of pentobarbital sodium U.S.P. in a dose of 0.44 cc. per kilogram of body weight. The conjunctiva and cornea were cocainized, after irrigation with a solution of benzalkonium chloride U.S.P. ("zephiran chloride"), 1:2,000. Diphtheroids were grown for twenty-four hours on proteose 3 agar, washed off with saline solution and immediately diluted and shaken to break up clumps. Standardized suspensions were prepared in mucin and in saline solution and plated to determine the viable count, as described later.

Production of Toxin by Diphtheroids.—A variety of methods was employed in an effort to demonstrate the production of toxin by diphtheroids. Among these were the Dolman[18] technic for staphylococcus toxin and Wadsworth medium II for production of toxin by diphtheria

16. Rother, W.: Ueber Farbstoffbildung bei zwei Xerosestammen, Centralbl. f. Bakt. (Abt. 1) **90**:127, 1923.

17. Herrenschwand, F.: Die pathogenen Mikroorganismen des Auges, Berlin, Urban & Schwarzenberg, 1927, p. 296. Benjamin, J., Jr.; Belt. E., and Krichesky, B.: Total Prostatectomy in the Rabbit and Intra-Ocular Transplantation of Prostatic Tissue, J. Urol. **44**:109, 1940. Gilbert, W., and Plaut, F.: Ueber Kammerwasseruntersuchung, Arch. f. Augenh. **90**:1, 1921.

18. Dolman, C. E.: Pathogenic and Antigenic Properties of Staphylococcus Toxin, Canad. Pub. Health J. **23**:125, 1932.

bacilli.[19] When these failed, we turned to the newly developed synthetic medium of Mueller and Miller[20] and Pappenheimer and Johnson.[21] The formula selected, 10 per cent casein hydrolysate with dextrose in place of maltose, 0.1 per cent agar and 0.3 microgram of ferrous sulfate per cubic centimeter, gave profuse growth of diphtheroids. After eight days' cultivation, Seitz filtrates were prepared and tested for hemolytic activity, dermonecrosis and capacity to injure the deeper tissues of the rabbit eye. They were stored at —77 C. in a carbon dioxide snow refrigerator until used.

EXPERIMENTAL RESULTS

Studies in Vitro.—Before investigating the effects of mucin on the pathogenicity of diphtheroids, we determined whether or not the substance supports their growth in vitro. Granular mucin[22] was suspended in buffered saline solution, according to the method of Rake,[23] and clarified by contrifugation. After several samples were tested for viscosity, lot 3111, in a final concentration of 3 per cent, was found suitable.

A forty-eight hour old culture was washed off from proteose 3 agar and diluted in one series with buffered saline solution and in another with buffered mucin solution. The bacterial suspensions were incubated at 37 C. and shaken thoroughly with beads in a Kahn shaking machine to break up clumps. At frequent intervals during a period of twenty-four hours, samples were removed, diluted and again shaken. Aliquots of 0.05 cc. were plated on proteose 3 agar in order to determine the total number of viable bacteria. These tests were performed in triplicate, and crowding of colonies was avoided.[24] The logarithms of the number of viable bacteria were plotted against time (in hours) on semilogarithmic paper and the growth curves compared.

As seen in figure 2, when the diphtheroids were cultivated in a menstruum of mucin, their growth curve shows an initial stationary phase, a lag phase, a logarithmic phase, a phase of negative acceleration and a

19. Wadsworth, A. B., and Wheeler, M. W.: Toxigenesis of Diphtheria Bacillus, J. Infect. Dis. **55**:123, 1933.

20. Mueller, J. H., and Miller, P. A.: Production of Diphtheric Toxin of High Potency (100 IF) on a Reproducible Medium, J. Immunol. **40**:21, 1941. Mueller, J. H.: The Influence of Iron on the Production of Diphtheria Toxin, ibid. **42**:343, 1941.

21. Pappenheimer, A. M., Jr., and Johnson, S. J.: Studies in Diphtheria Toxin Production: III. A Simple Gelatin Hydrolysate Medium and Some Properties of the Toxin Produced Thereon, Brit. J. Exper. Path. **18**:239, 1937

22. The mucin, 1701, was prepared by the Wilson Laboratories, Chicago.

23. Rake, G.: The Mouse Protection Test in the Standardization of Anti-Meningococcus Serum, Canad. Pub. Health J. **28**:265, 1937.

24. Wilson, G. S.: The Proportion of Viable Bacteria in Young Cultures with Especial Reference to the Technique Employed in Counting, J. Bact. **7**:405, 1922.

maximum stationary phase, thus resembling a standard bacterial growth curve.[25] Hence, mucin is a suitable medium for the growth of diphtheroids. Buffered saline solution, on the other hand, is not suitable, as shown by a decreasing bacterial population from hour to hour.

Studies in Vivo.—Suspensions of diphtheroids in mucin cause a much earlier, more intense and more enduring inflammatory reaction than similar doses made up in saline solution. Thus, when several million bacilli

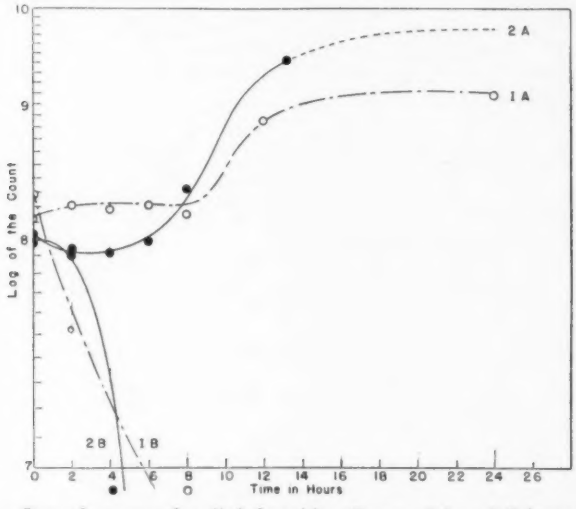

Fig. 2.—Growth curves for diphtheroids: Curves 1*A* and 2*A* represent results of two separate experiments performed with bacilli suspended in mucin; curves 1*B* and 2*B*, results of analogous experiments with diphtheroids suspended in saline solution.

were injected in a menstruum of saline solution into the anterior chamber of albino rabbit eyes, there was little cytologic reaction, and few bacteria were seen in the aqueous humor, which was removed at varying intervals up to three days and stained by means of supravital staining and the Giemsa and Gram stains. With similar doses of bacteria suspended in mucin, there was, after a lag of about ten hours, a prolific exudate, consisting largely of neutrophils (70 to 90 per cent) and a varying number of lymphocytes and histiocytes. Diphtheroids were also much more numerous. After two to three days, both cells and bacteria began to decrease in number. Similar experiments were performed in the abdominal cavity of mice, where the phenomenon could be studied with greater facility. It was clearly demonstrated that mucin favors the multiplication and survival of the stain of diphtheroids under investigation.

25. Buchanan, E. R.: Growth Curves of Bacteria, in Jordan, E. O., and Falk, I. S.: Newer Knowledge of Bacteriology and Immunity, Chicago, University of Chicago Press, 1928, p. 46.

TABLE 1.—*Clinical and Pathologic Observations After Intraocular Injection of Diphtheroids (Dose, 100,000 Viable Bacilli) Into Anterior Chamber of Albino Rabbits**

Rabbit No.	Eye	Clinical Observations	Histopathologic Observations
		Series E: Living Culture Suspended in Mucin	
48	R	Intense congestion of lower edge of ciliary body and ora; cornea clear	Congestion and polymorphonuclear cell exudate at corneoscleral junction; scant purulent exudate in anterior chamber
49	R	Opacity of cornea and lens; pupil dilated; limbus and ciliary body engorged	Large recent organizing hemorrhage at one corneoscleral junction; polymorphonuclear cell exudate in filtration angle and anterior chamber
50	R	Cornea hazy; ora slightly congested	Fibroblastic proliferation at both corneoscleral junctions; old polymorphonuclear cell exudate; swelling of endothelial cells and macrophages; reaction extending into base of ciliary body; proliferation of corneal and ciliary epithelium
29	R	Cornea wrinkled and hazy; irregular projections from iris into pupillary area; engorgement of ciliary body	Small amount of recent hemorrhage at one corneoscleral junction; veins and lymphatics dilated; eosinophilic exudate; vessels dilated at opposite angle
30	R	Small opacity at edge of iris; slight opacity near lower area of limbus; ora slightly congested	One corneoscleral angle normal except for slight dilation of vessels; at other, cornea greatly thickened by edema and a considerable eosinophilic exudate; vessels dilated
31	R	Pupil large; cornea wrinkled and slightly hazy; opaque spot in pupillary area; ora congested; small opacity on lens	At one corneoscleral angle and, to less extent, in opposite angle, dilatation of vessels and slight polymorphonuclear cell and lymphocytic exudate; at angle of anterior chamber and iris on most involved site of cornea, purulent exudate with edema of iris
		Series F: Living Culture Suspended in Saline Solution	
29	L	Cornea slightly hazy; ciliary body congested	Occasional eosinophilic polymorphonuclear leukocyte in undilated vessels; moderate congestion of some ciliary processes
30	L	Cornea clear; corona engorged at inner edge	Normal
31	L	Pupil large; cornea clear; corona slightly congested	Ciliary bodies irregularly congested
49	L	Cornea clear; pupil large; congestion of ora	Small hemorrhage in one fold of ciliary process
48	L	Cornea clear; pupil small; slight congestion of lower edge of ciliary body	Congestion and pyknotic nuclei at one corneoscleral junction
50	L	Cornea clear; pupil normal; slight congestion of ora; one large, heavily engorged area of retina at lower edge of ora	Edema, necrosis and a little corneal epithelial proliferation at one spot

Smaller doses, 100,000 to 200,000 bacilli, were employed in a detailed clinical and pathologic study of the pathogenicity of diphtheroids. Heat-killed suspensions of bacteria and control doses of mucin alone were similarly inoculated into the anterior chamber of albino rabbit eyes in a volume of 0.1 cc. In this way, the foreign protein factor and the effects of mucin per se could be evaluated. In tables 1 to 3 are presented

TABLE 1.—*Clinical and Pathologic Observations After Intraocular Injection of Diphtheroids (Dose, 100,000 Viable Bacilli) Into Anterior Chamber of Albino Rabbits*—(Continued)*

Rabbit No.	Eye	Clinical Observations	Histopathologic Observations
		Series G: Killed Bacteria Suspended in Mucin	
54	R	Cornea clear; pupil normal; ora congested	Edema at periphery of corneoscleral junction on both sides; congestion and recent hemorrhage; polymorphonuclear cell exudate; old fibroblasts, macrophages and lymphocytes from corona into ciliary body
55	R	Cornea clear; pupil normal; ora heavily engorged	Normal
56	R	Cornea clear; pupil small; slight congestion of ora	Collection of fibroblasts and degenerating polymorphonuclear cell at one corneoscleral junction and barely perceptible at the other
32	R	Normal	Small area limited to cornea at corneoscleral angle, which is infiltrated with polymorphonuclear cells and lymphocytes; irregular congestion and edema of ciliary folds
32	L	Normal	Reaction similar to that in right eye of rabbit 32
		Series H: Killed Bacteria Suspended in Saline Solution	
54	L	Cornea clear; pupil large; slight congestion of ora	Tiny area of necrosis and fibroblastic proliferation, apparently needle tract
55	L	Cornea clear; pupil large; opacity at periphery of lens; ora heavily engorged	Small collection of fibroblasts and old polymorphonuclear leukocytes at corneoscleral junction
56	L	Cornea clear; pupil small; heavy engorgement of cornea	Ciliary processes moderately congested

*Observations were made at the end of forty-eight hours.

extracts from daily protocols, as well as results of histologic examinations made after enucleation of the animals' eyes. It will be seen (figs. 3 and 4) that, whereas mild inflammation of the cornea and uveal tract occurs as the result of intraocular injection with diphtheroids suspended in saline solution, the reaction is much severer and lasts much longer when a menstruum of mucin is used. Mucin also increases the irritant

action of killed bacilli. This is noteworthy, since when injected alone into the anterior chamber it is virtually innocuous.

TABLE 2.—*Clinical and Pathologic Observations After Intraocular Injection of Diphtheroids (Dose, 105,000 Viable Bacilli) Into Albino Rabbits**

Rabbit No.	Eye	Clinical Observations	Histopathologic Observations
		Series A: Living Culture Suspended in Mucin	
52	R	Cornea wrinkled, protruding and opaque; circumcorneal vessels engorged; pupil very large; ora congested	At both edges of cornea, extensive congestion, hemorrhage and polymorphonuclear exudate; fibroblastic proliferation, macrophages and edema; reaction extends to base of ciliary body
51	R	Cornea clear, wrinkled at edge of limbus; long, thin opacity in midline; hypopyon at lower edge of cornea; congestion of vessels; engorgement of ora and iris; detachment and heavy engorgement of retina; pupil large	Section unsatisfactory
53	R	Cornea thickened and wrinkled, with opacity in midline; congestion of circumcorneal vessels; ora extremely congested and heavily engorged; two areas of discoloration on retina	Similar to reaction in right eye of rabbit 52
		Series B: Living Culture Suspended in Saline Solution	
51	L	Cornea slightly hazy; pupil normal; engorgement of ora	Normal
52	L	Cornea clear; pupil large; slight congestion of ora	Slight focal edema and necrosis and endothelial swelling at periphery of cornea
53	L	Cornea clear; pupil small; ora congested	Practically normal; focal edema in sclera at corneoscleral junction
		Series C: Killed Bacteria Suspended in Mucin	
59	R	Cornea clear; slight congestion of ora; area of discoloration of retina at lower edge of ora	Recent small hemorrhage into ciliary processes; one corneoscleral junction showing barely perceptible focus of a few degenerated polymorphonuclear cells and fibroblasts; apparently needle tract
57	R	Cornea clear; slight congestion of ora; two small areas of congestion at lower edge of ora on retina	At one corneoscleral junction, small collection of lymphocytes; on opposite side, recent hemorrhage in ciliary process
58	R	Cornea clear; pupil normal; slight congestion of ora; two areas of congestion on retina	At corneoscleral junction, lymphocytes and fibroblasts, extending into ciliary body; vessels dilated; recent hemorrhage into ciliary process

The ocular lesions which were produced by diphtheroids usually regressed spontaneously during the course of two to three weeks.

It must be emphasized that the pathogenicity of diphtheroids was demonstrable only when the interior of the albino rabbit eyes was used as the test medium. No untoward effects were observed after subconjunctival or intradermal injection into rabbits or after intracerebral or intra-abdominal inoculation of mice. Absence of invasive power was

TABLE 2.—*Clinical and Pathologic Observations After Intraocular Injection of Diphtheroids (Dose, 105,000 Viable Bacilli) Into Albino Rabbits* —(Continued)*

Rabbit No.	Eye	Clinical Observations	Histopathologic Observations
		Series D: Killed Bacteria Suspended in Saline Solution	
57	L	Cornea clear; three small areas of discoloration on retina	Small, dense collection of lymphocytes and fibroblasts at both corneoscleral junctions
58	L	Cornea clear; ora engorged	Small hemorrhage into ciliary process at opposite corneoscleral junction
59	L	Cornea clear; pupil very large; ora congested; slight discoloration at edge of ora on retina	Normal
		Series E: Mucin Only	
33	R	Bleb at corneoscleral angle	One side of ciliary body congested and small organized scar at iris
40	L	Normal	Small collection of lymphocytes in sclera of anterior part of eye
356	R	Normal	Small, recently organized scar at posterior surface of cornea at periphery
357	R	Normal	Recently organized scar of cornea
		Series F: Saline Solution Only	
		Ten animals given injections; all normal	normal

*Observations were made at the end of seventy-two hours.

established by Menkin's[26] technic. Large doses (10,000,000 bacilli) were suspended in mucin and in saline solution and injected intracutaneously into the foreleg of rabbits. Twenty-four hours later the axillary lymph nodes, spleen, liver and heart's blood were cultured, but no diphtheroids could be isolated.

26. Menkin, V.: Invasiveness and Virulence in Relation to Resistance, J. Infect. Dis. **58**:81, 1936.

TABLE 3.—*Clinical Observations After Injection of Diphtheroids (Dose, 200,000 Bacilli) Into Anterior Chamber of Albino Rabbits**

Rabbit No.	Eye	Living Culture in Mucin	Rabbit No.	Eye	Killed Culture in Mucin
337	R	Cornea milky, opaque; iris invisible; chemosis of cornea; crusting of lids; scleral vessels congested; circumcorneal red band; lower palpebral conjunctiva more congested than upper, which is only slightly so	337	L	Circumcorneal vessels slightly congested; irregular inner margin of iris with fibrinous exudate; striae of iris slightly pink
338	R	Conjunctivia congested, lids red, cornea slightly cloudy; no reaction to light; hypopyon, fibrinous exudate, iris markings cannot be seen	338	L	Normal, except slight irregularity of inner margin of iris at one point
349	R	Lids red, moist, swollen; crusty, with slight discharge; conjunctival sclera and circumcorneal vessels congested; pupils reactive to light; cornea faintly cloudy, iris markings broadened into red bands	349	L	Normal
340	R	Lids slightly pink with slight discharge; palpebral conjunctiva slightly congested, chemosis of cornea, circumcorneal vessels forming tortuous reddish band; severe iritis; irregular margin and fibrinous exudate at one point remaining	340	L	Normal, except for slight irregularity of inner margin of iris at point of inoculation
341	R	Pronounced exophthalmos; cornea chemotic; lids slightly crusty with slight white, mucoid discharge; no reaction to light; conjunctiva normal; congestion of circumcorneal vessels to form band; scleral vessels not noticeable; cornea faintly cloudy; very severe iritis	341	L	Normal
342	R	Lids crusty with slight opaque, white discharge in conjunctiva; chemosis and haziness of cornea intense; hypopyon; circumcorneal vessels congested, forming bright red band	342	L	Cornea faintly cloudy; iris markings red; circumcorneal vessels and lower conjunctiva congested
		Living Culture in Saline Solution			Killed Culture in Saline Culture
343	R	Exophthalmos and chemosis of cornea pronounced; mucoid discharge from conjunctiva; photophobia; no reaction to light; lids red and slightly edematous; conjunctival vessels congested; scleral and circumcorneal vessels congested; cornea milky and opaque	343	L	Normal
344	R	Iritis; enlargement of striae; some broad, others less so, but considerable increase; reacts to light slowly; fibrinous exudate	344	L	Normal
345	R	Very mild iritis	345	L	Normal
346	R	Very mild iritis	346	L	Normal
347	R	Slight iritis	347	L	Normal
		Mucin (Control)			Saline Solution (Control)
355	R	Normal	355	L	Normal
356	R	Normal	356	L	Normal
357	R	Normal	357	L	Normal

*Observations were made after six days.

Suspensions of diphtheroids, made up in saline solution or mucin, were also instilled into the nostrils of mice which had been lightly anesthetized with ether. These bacteria could not be recovered from any of the viscera or the heart's blood twenty-four hours later.

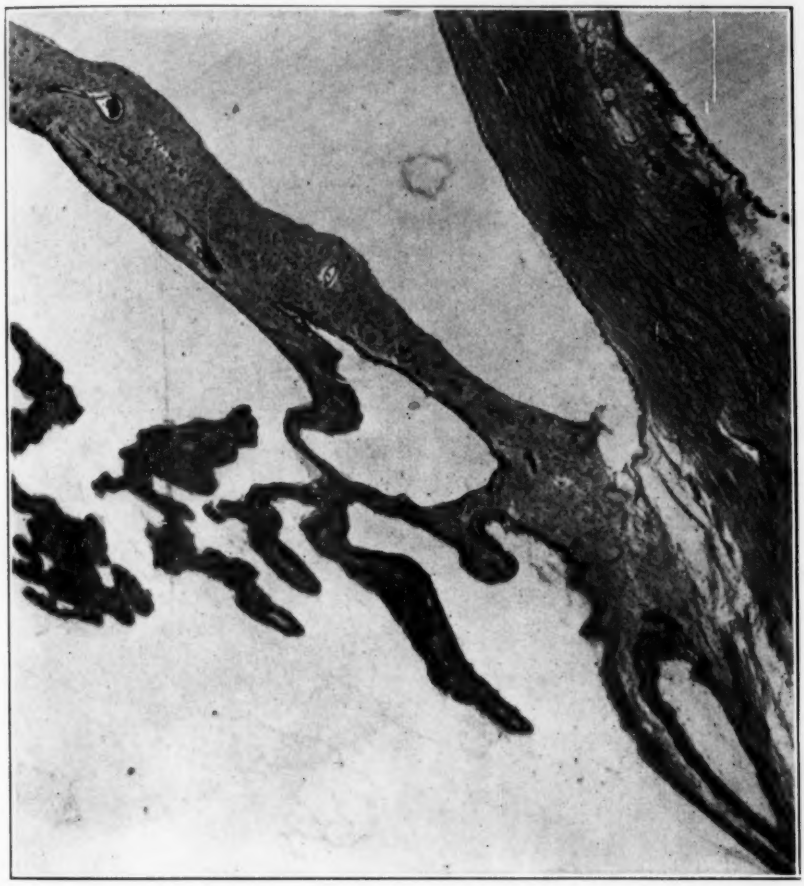

Fig. 3*A* (rabbit 52).—Histologic section of left eye obtained seventy-two hours after injection of diphtheroids (suspended in saline solution) into anterior chamber. There are slight focal edema and necrosis and endothelial swelling at the periphery of the cornea.

DEMONSTRATION OF TOXIC FILTRATES IN CULTURES OF DIPHTHEROIDS

Sterile filtrates which were prepared by the Pappenheimer and Johnson method[21] were inoculated into the anterior chamber of 9 anesthetized albino rabbits. As seen in the protocols cited here, the filtrates produced moderately severe inflammation of the iris and cornea in 7 of the animals. These lesions cleared in a week or two. Filtrates which had been boiled for ten minutes were harmless.

These filtrates were not hemolytic for rabbit, sheep or human erythrocytes. No signs of necrosis were demonstrable after intracutaneous or subconjunctival injection into rabbits or guinea pigs. Likewise, intravenous injection into these animals and intracerebral or intra-abdominal inoculation of white mice were without effect.

Fig. 3*B*.—Right eye, after a similar injection of diphtheroids suspended in mucin solution. There are extensive congestion, hemorrhage and a polymorphonuclear cell exudate at both edges of the cornea, as well as fibroblastic proliferation and edema. The reaction extends to the base of the ciliary body. (Zeiss ocular; × 120).

PROTOCOL.—Filtrate 129 AB, 0.1 cc., injected March 9, 1944 with the animal under pentobarbital anesthesia.

RABBIT 7A.—Twenty-four Hours After Injection: Eye closed; slight opacity of cornea; markings of iris not visible; plastic exudate at inner edge of iris.

Seventy-Two Hours: Band composed of bright red blood vessels at limbus and congestion of palpebral conjunctiva.

Five Days: Eye essentially normal.

RABBIT 79.—Twenty-Four Hours: Circumcorneal vessels congested, forming bright red band at limbus; vessels of bulbar conjunctiva also congested; slight iritis.

Seventy-Two Hours: Iritis persists (disappeared three days later).

RABBIT 80.—Twenty-Four Hours: Plastic iritis; congestion of palperbral vessels; episcleritis.

Seventy-Two Hours: Congestion of palpebral conjunctiva and circumcorneal vessels; mild iritis.

Six Days: Eye normal.

RABBIT 82.—Forty-Four Hours: Cornea, the color of mother of pearl; congestion of circumcorneal and palpebral vessels.

Five Days: Corneal opacity persisting; suggestion of keratoconus.

Eight Days: Eye clearing.

PROTOCOL 2.—Filtrate 130, prepared April 5, 1944; injected May 1, 1944 with animal under pentobarbital anesthesia; dose, 0.1 cc.

RABBIT 7B.—Three Days After Injection: Lids edematous; circumcorneal vessels red; intense opacity of cornea; iris obliterated; pupil not reactive to light.

Seven Days: Three quarters of cornea opaque; iris barely seen; pupil not reactive to light; edema of nictitating membrane; beginning of pannus.

RABBIT 10.—Three Days: Lids and conjunctiva inflamed; exophthalmos; cornea opaque; loss of light reflex; iris markings obliterated.

Seven Days: Cornea opaque; pannus progressing; lid margins red; pupillary reaction to light sluggish.

RABBIT 11.—Three Days: Eye protruding; cornea opaque; loss of pupillary reflex.

Seven Days: Cornea showing milky, white opacity and resembling keratoconus; iris markings not seen.

COMMENT AND SUMMARY

Diphtheroids, resembling C. xerose, which were isolated from the human conjunctiva, grew well in a menstruum of mucin. Similarly, when suspended in this medium and inoculated into the anterior chamber of the eyes of albino rabbits, cultures retained their viability in vivo for several days, while in suspensions in saline solution they were rapidly destroyed.

Intraocular injection of diphtheroids suspended in saline solution into albino rabbits produced moderate inflammation of the ciliary process. When suspended in mucin, the reaction lasted longer, was much severer and was associated with acute keratitis. The lesions usually regressed spontaneously within two or three weeks.

While suspensions of killed cultures of diphtheroids in saline solution produced mild inflammatory changes in the ciliary process, which

were seen in histologic sections, none was visible grossly. Suspensions in mucin produced severer inflammatory reactions. Since mucin by itself is relatively innocuous, it is suggested on the basis of these studies, and those of others,[27] that it protects bacteria from the digestive actions of humoral and cellular proteolytic enzymes and other immunologic defense mechanisms. Living diphtheroids are thus permitted to grow and exert their pathogenic activity.

By applying the recently developed methods of Mueller and Miller and Pappenheimer and Johnson, it was possible to demonstrate that a filtrate which is produced by growing diphtheroids in a medium of very low iron concentration is injurious to the uvea and cornea, but not to the skin or conjunctiva of albino rabbits.

On the basis of these investigations, it may be concluded that diphtheroids which are almost constantly present on the normal and inflamed human conjunctiva may be considered as potential pathogens, which may exert injury when they are introduced into the interior of the eye.

Jewish Hospital, Philadelphia (Dr. Weiss).

Departments of Bacteriology (Miss Shevky) and Pathology (Dr. Perry), University of California, San Francisco.

27. Komarov, S. A.: The Influence of Mucoitinsulfuric Acid on Peptic Digestion, Am. J. Digest. Dis. **3**:164, 1936. Miller, C. P.: A Study of Experimental Meningococcus Infection, Proc. Soc. Exper. Biol. & Med. **32**:1136, 1935.

CONTAMINATED OPHTHALMIC OINTMENTS

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OPHTHALMIC OINTMENTS have been, and are, prescribed and used by ocular surgeons throughout the civilized world. By far the most commonly used by the family physician is yellow mercuric oxide. The American lay public long used this ointment as a household remedy for external diseases of the eye; it is now to be replaced by sulfathiazole ointment. In the experience of one of us (L. L.), the same collapsible tube containing an ointment of mercury bichloride U.S.P., boric acid ointment U.S.P. or ammoniated mercury ointment U.S.P has been used in the treatment of numerous patients in office practice, with a thought to economy, until the last wormy drip has been expressed. At the Wills Hospital, it was our experience for years to use an ointment containing mercury bichloride (1:3,000) after all cataract operations, merely because we had seen our predecessors use the same technic. Not more than seven years ago, we witnessed a corneal transplantation by a well known surgeon of New York in which he squeezed a goodly portion of an ointment from a collapsible tube into the patient's eye for antisepsis and lubrication. On another occasion, we saw motion pictures of a transplantation performed by the same surgeon in which he advocated the use of sulfathiazole, 5 per cent, immediately after the operation and then, at a later period, penicillin ointment.

Most ophthalmic surgeons and students of ophthalmology are inclined to play "follow the leader." It is not good form to question the masters who have obtained good results. But personal experience with a succession of infections following operations makes the surgeon stop to recount his steps in an effort to discover the missing link in asepsis and antisepsis. Our attention was directed to the use of ointments in general. Dismissing at once the old ointment jar, we directed our study toward the sterility and the maintenance of sterility of ointments commonly used in

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collapsible tubes. It is our experience that the first sample of the ointment expressed from a fresh tube, regardless of the name of the ointment, differed in color and consistency from the second. It was also found that the nozzle of the tube was never free from ointment after a quantity had been expressed. Pressure by the fingers seemed to leave a wormlike protrusion at the tip of the tube, over which the cap was replaced. This overflowing quantity of ointment remained in the cap and on the nozzle of the tube until the next use. Not always is it customary to express a quantity on a towel or a pledget of cotton before the second toothpaste-like ribbon is inserted into the eye. In other words, the ophthalmologist has a false sense of security that the ointment in every collapsible tube is sterile until the last bit is squeezed out. It has been the belief that the contents of the tube of ophthalmic ointment were sterile at the beginning and at the end. I feel certain that most ophthalmologists have used these ointments in the treatment of corneal ulcers with the belief that the germicidal value of its contents was sufficient to destroy the bacteria present.

Strangely, we ophtholmologists have never seen a collapsible tube of ophtholmic ointment marked "sterile;" yet for years we have ordered such ointments in the treatment of hordeolum, blepharitis marginalis, ulcerative keratitis and injuries to the eye, with a smugness founded on custom rather than on scientific knowledge, in the belief that healing qualities of ointments were guaranteed by every textbook on ophthalmology. Fisher, Accousti and Thompson[1] reported from the Warner Institute for Therapeutic Research that ointments containing 5 per cent sulfanilamide, sulfathiazole or sulfadiazine in a water-dispersible base may become contaminated with disease-producing organisms which these sulfonamide compounds are not capable of killing.

PRESENT INVESTIGATION

We wish to present evidence that most ophthalmic ointments in new and unused tubes are sterile. We wish to prove that once a fresh tube is opened the remaining contents are frequently contaminated.

Culture Mediums.—The culture medium used in this experiment was brain-heart infusion agar with sterile human blood. Approximately 1 inch (2.5 cm.) of sample was expressed from each collapsible tube on to the culture medium. The period of incubation varied from one week to ten days. The first culture appeared within forty-eight to seventy-two hours. The incubation temperature was 37 C. The ophthalmic ointments used in this series of experiments were obtained from six manufacturers.

Ointments Cultured.—Cultures were made of the contents of 50 used tubes and 24 unused tubes of commonly known ophthalmic ointments as found on the

1. Fisher, C. V.; Accousti, N. J., and Thompson, M. R.: Bacterial Contaminations in Sulfonamide Ointments, J. A. M. A. **122**:855-858 (July 24) 1943.

open market. Three control Petri dishes were also observed, the mediums having been exposed for the same length of time as that required to inoculate the mediums.

Used Tube Cultures: Of the 50 tubes which had been used more than once, a goodly proportion showed contamination with bacteria, such as Staphylococcus albus hemolyticus, Staphylococcus aureus hemolyticus, fungi (species not determined) and other organisms which were not identifiable by microscopic examination alone.

Of 15 tubes of 5 per cent sulfathiazole ointment which had been used at least once, 8 yielded growth. Of 11 tubes of an ointment containing mercury bichloride (1:3,000), 4 were contaminated. Of 5 tubes of penicillin ointment (500 units per gram), 2 samples yielded growth. Of 7 tubes containing epinephrine bitartrate which had been opened once or more, 2 yielded pathogenic organisms. One of 6 tubes of atropine sulfate ointment which had been used yielded growth. Three tubes of ointment containing tetracaine hydrochloride were found to be sterile. A tube of ointment containing physostigmine salicylate, 1 per cent, which had been used for patients postoperatively showed many fungi. One borofax[R] tube[2] was sterile.

Unused Tube Cultures: Twenty-four new tubes of ointment were selected from a stock pile of boxes containing 5 per cent sulfathiazole ointment. One tube was selected from each supply box as a spot check, each box having 50 small tubes of 1/8 ounce (3.8 Gm.) each.

In 12 new, unused tubes the first portion of ointment was cultured; no sample yielded growth. In another group of 12 new tubes, the entire contents of each tube was cultured; that of 1 tube contained organisms. Three controls, consisting of blood agar, were exposed for the same length of time as that required to smear the ointment from the tube. The three controls were sterile on culture, indicating there was no contamination from the outside atmosphere during the period of exposure.

Comment.—There was sufficient evidence from all the experiments to indicate that the unused tube of ointment was in most instances sterile, whereas the used tubes were frequently contaminated.

The observations in this study call for a revaluation of the use of ophthalmic ointments in the eye after operation and of the use of ointments for ophthalmic conditions in general.

We appreciate the difficulty of sterilizing ophthalmic ointments The composition of the tubes and that of the ointments enter into the difficulty of marketing or preparing sterile ointments in collapsible tubes.

CONCLUSIONS

We have no proof that infections actually occur from the use of contaminated ointments. Surgeons of experience, however, do not wish to

2. Borofax contains 10 per cent boric acid in an ointment base.

publicize overwhelming evidence in the form of blind eyes. We do not have proof that the organisms found in the contamination were pathogenic bacteria. The mere fact that the ointments contain organisms is sufficient proof that pathogenic bacteria may also be present. One may question why more infections do not occur from the use of ointment in used tubes. The answer can be only a conjecture. Either the lysozymes of the tears have their effect on certain bacteria or the eye itself possesses a factor, *X*, which saves most patients from infection following intraocular operation. Scientists do not willingly or knowingly place contaminated ointments into open wounds, not even into a healthy eye.

Our experiments have led us to discontinue the postoperative use of ointments. We get along very well without them. Perhaps we, too, were formerly the subjects of habit and custom.

We were greatly surprised to learn that sulfathiazole ointment and penicillin ointment may become contaminated before the contents of the tube are exhausted. We have lost faith in the use of ointments. Our confidence can be restored only if an ointment could be produced sterile in containers for one application only. It is hoped that the experiments here reported may stimulate renewed interest in ophthalmic therapeutics.

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DISCUSSION

DR. LOUIS GERSHENFELD, Philadelphia: We are indebted to Dr. Lehrfeld and Dr. Donnelly for the presentation of this paper on the sterility of ointments. In general, information like this comes from laboratory workers, and perhaps does not attract the attention of the rank and file of physicians. It certainly does not reach the ophthalmologist with the same impressiveness and significance as it does when coming from the ophthalmic surgeon. This paper should arouse interest.

I recall distinctly that about twenty-five years ago I was much concerned about the sterility of ampules, in particular those used for internal medication. It happened that I was at a meeting with the Commissioner of Food and Drugs. As you know, the Food and Drug Administration is interested primarily in the traffic of food and drugs as it is concerned with interstate commerce. During the discussion I asked Mr. Campbell, the commissioner, whether the members of his department had examined ampules on the open market. He did not recall at the time and turned to two of his assistants. They replied that they did not think so. I then said, "Don't you think it would be of more interest, and certainly of greater value, if one were concerned with the examination of ampules on the market, especially the sterility of solutions for parenteral injection, than with routine matters, such as whether the strychnine content of nux vomica is 1.15 or 1.05 per cent?" The latter is important, but it is of greater importance to be sure that solutions which are injected directly into the system, and sooner or later reach the blood stream, are sterile. I was surprised to learn that the Food and Drug Administration was not concerned in determining the sterility of products. My attention at the time was directed to this matter because a prominent internist had

asked me to examine three similar ampules which he had. I found in each a hemolytic Staph. aureus, which produced suppuration in rabbits. He had suspected that something was wrong, since injections of the other 9 ampules had produced abscesses in 4 patients. The other patients never came back, and he was wondering what was the matter. I immediately wrote an editorial in one of the journals, and it was at that time that the Food and Drug Administration proceeded to spend over $25,000 in looking into the sterility of solutions for parenteral use throughout the country.

I, too, then began to examine the ampules on the market. Few stated that they were sterile. There was a statement as to contents, such as a solution of iron citrate or a solution of morphine sulfate.

More recently, as a member of the Sterile Advisory Board of the United States Pharmacopeia, I became concerned with the sterility of many of these products. Now we define a solution for parenteral injection, and therefore ampules and solutions for such use must be sterile, whether labeled so or not. The Food and Drug Administration and the manufacturers accept this policy. As a result, this class of marketable products is sterile, and we have had practically no trouble from that angle.

On the other hand, ointments are not sterile unless they are so labeled. I dare say that there are few sterile ointments on the market, whether used for ophthalmologic or other surgical work. I have examined ointments in tubes and in jars and have found them revealing the presence of bacteria.

The whole question of sterility is intricate and frequently complex. One must bear in mind, of course, that there is the matter of price; the economic question affects the picture. I, for one, have always stated that the question of price should not enter into the consideration if one wants a finished preparation which one feels assured is sterile. I recall when surgical gut became official in the "Pharmacopeia." At that time I, and members of our committee, went on record as stating that individual strands should be kept in individual hermetically sealed glass tubes. This form of marketing was first official in the twelfth edition of the "Pharmacopeia," and it is official in the thirteenth edition. At one time many strands were kept in one container. This was objectionable, for the same reasons that Dr. Lehrfeld has presented.

Now, with respect to ointments, one must bear many facts in mind. Dr. Lehrfeld mentioned various ointments which for the moment one might think were bactericidal. However, this is not always the case. The sulfonamide compounds, for instance, are only bacteriostatic; they are not bactericidal. They do not kill even if used internally, let alone when applied in ointments. One is prone to forget that when one speaks of a bactericidal effect one may think that all species of micro-organisms are killed. That is not so. The sulfonamide compounds are effective only against certain groups of organisms. The same holds true for penicillin. Even in the case of a bactericidal agent which is effective in suitable liquids, one will find that in ointments, unless the proper base, a water-miscible or a water-soluble base, is used, one may not get the same bactericidal or bacteriostatic effect; that is true, for instance, with phenol. A phenol ointment in a petrolatum base will have little antibacterial effect, but with a water-miscible base an entirely different effect is obtained.

As to the containers for ointments, I, for one, heartily endorse Dr. Lehrfeld's recommendation that certainly after operation a tube or container should be used only once for an open wound. If an ointment is to be used in ophthalmic surgery, it should certainly be sterile. Of course, the proper method of sterilization must be practiced. This may be difficult. It is not a simple procedure to market sterile ointments in small tubes or other individual containers unless the expense is considered, for it is an intricate, tedious, long-drawn-out process. The ointment tube itself, even the tubes for ophthalmic use, are generally primarily tin. Some of them contain about 0.75 per cent copper, added for hardening purposes. In the larger tubes of ½, 1 or 4 ounce (15, 30 and 120 Gm.) capacity and larger, usually not used for ophthalmic products, lead, lined with tin, 7 per cent, is employed, and for toothpaste tubes 3 per cent tin is used. Some tubes may even have a plastic lining, but not the tubes for ophthalmic use.

It must be remembered that all tubes must be sterilized. The ophthalmic tubes of pure tin with the small amount of copper can withstand heat up to 400 F. My colleagues and I use dry heat at 160 C. (320 F.) for sterilization. The closures are generally of "bakelite," which may hold up at this temperature. The individual sterile tubes, then, must be filled with the sterile ointment under aseptic conditions. In many instances it may not be practical to sterilize the tube and contents or the final containers.

One may, of course, have individual sterile gelatin containers. All this means additional cost for the manufacturer. I assure you the pharmaceutical firms are willing to cooperate, but they consider the cost made necessary by the expense in producing such a preparation.

The question has been raised whether a bacteriostatic or bactericidal agent may be added which, when incorporated into an ointment, will result in a preparation that is self sterilizing. Zinc peroxide has been mentioned. This substance may be satisfactory, but in some instances it possesses irritating effects, especially in the eye. Urea peroxide has been recommended for sulfonamide ointments, but on standing the sulfonamide compound frequently becomes oxidized. The self-sterilizing agent not only must kill bacteria which are present but must be nonirritating; so a series of tests to prove that particular point must be conducted. Furthermore, one cannot usually say that because the zinc peroxide or the urea peroxide is effective in combination with the sulfonamide compounds it will be effective with other medicaments. The question of such factors as effectiveness, stability and harmlessness must be considered.

I recommend and heartily endorse individual containers for dispensing ophthalmic ointments, certainly for preparations used for surgical purposes. However, unless requests for sterile ointments are made specifically, unless there is a demand for them and unless individual physicians are willing to meet the additional expense involved, manufacturers will not market sterile ointments for use in ophthalmologic surgery.

Dr. George Dublin, Philadelphia: My comments have to do with the effects of ordinary ophthalmic ointments on the eye. For many years I have noted untoward actions to the use of ophthalmic ointments. These reactions were noted particularly in cases in which foreign bodies had

been curetted from the cornea, and, as usual, an ointment containing tetracaine hydrochloride U.S.P. or butacaine sulfate U.S.P. was ordered. The corneal abrasion healed without much trouble, but I noticed a considerable number of punctate areas over the cornea which stained with the dye; these areas persisted for several days after the healing of the original corneal ulcer or the corneal abrasion.

At first, I thought that these abraded areas were due to a form of allergy. Later, it occurred to me that they might be due to mechanical irritation. There is no ointment in which the drug is completely dissolved; some of it remains in crystal form. The small crystals within the ointment, by their mechanical action, cause corneal abrasions.

At first, I wondered why these patients complained of vague symptoms such as scratchiness, a sensation of a foreign body and tearing in the presence of a quiet eye, until I routinely stained each patient's cornea with fluorescein sodium; to my surprise, I found a great number of staining areas. To eliminate the possibility that these reactions were allergic, I used these ointments in the fellow eye and noted the same reaction. I tried other types of ointments, and I found that, regardless of the type I used, even boric acid ointment, I got the same reaction in a great majority of cases. I felt that an abraded cornea, the result of the use of an ophthalmic ointment, is an excellent medium in which infection may develop. I reasoned that, instead of preventing an infection, I might be responsible for the development of a corneal ulcer. I have noted these reactions for several years; consequently, I have not used ophthalmic ointment when I could avoid it, since, in my opinion, liquid medication is as efficacious as, and probably considerably better than, the use of ointment.

CLINICAL EXPERIMENTS WITH NEW WAYS OF INFLUENCING INTRAOCULAR TENSION

I. Effect of Rice Diet

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OPHTHALMOLOGISTS are far from understanding completely the mechanism of maintenance and regulation of the intraocular pressure. The supreme governing mechanism most probably consists in a combined action of hormonal and neural elements, similar to the pattern which exists with regard to the endocrine system.

Contradictory reports have been made concerning the influence on the intraocular pressure of the hormone of the posterior lobe of the pituitary gland. Franceschetti and Schläppi,[1] however, demonstrated that the increase or decrease of tension depends on the quantity of hormone in action. This shows how complicated the mechanism must be. Possibly other known or hitherto unknown substances may be involved.

The influence of the sympathetic and parasympathetic portions of the autonomic nervous system on various functions of the eyes has long been recognized. Hess[2] contributed further to knowledge of this action. From the charts recording his extremely interesting, and not yet published, results in producing a number of combinations of symptoms in various parts of the body by stimulation of minute circumscribed parts of the hypothalmus, it is evident that there is a definite area in the hypothalmus stimulation of which regularly produces a simultaneous rise in blood pressure and dilation of the pupil. Although Hess has not yet extended his experiments to the investigation of the intraocular pressure,

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1. Franceschetti, A., and Schläppi, V.: Die Wirkung der Hormone des Hypophysenhinterlappens auf die Pupille und den intraocularen Druck, Deutsche med. Wchnschr. **66**:529, 1940.

2. (*a*) Hess, W. R.: Vegetatives Nervensystem und Auge, Klin. Monatsbl. f. Augenh. **77**:289, 1926. (*b*) Hess, W. R., and Lehmann, F. E.: Der Einfluss vegetativer Reizstoffe auf der Adeptier unzustand der Retina, Arch. f. d. ges. Physiol. **211**:603, 1926.

it might be well to search for a regulatory center of this kind in that area.[3]

Thus, whereas there is a general idea how a central governing mechanism for the regulation of the intraocular tension might be organized, the existence of such a center is hypothetic. A rational way of influencing the intraocular tension through that center, therefore, is still a remote possibility.

Much more definite is knowledge concerning local factors which influence the intraocular tension. It is understood that these local factors are under the influence of the hypothetic center in the hypothalamus. This, however, does not exclude the possibility of acting on these factors independently or the usefulness of such an attempt so long as one is unable to control the whole problem from a central point.

In principle, the local mechanism in the eye which controls the intraocular tension centers around the balance of inflow and outflow of the intraocular fluid.

The inflow depends partly on the conditions existing on either side of the blood-aqueous barrier. Among these conditions, the osmotic pressure, which is dependent on the concentration of electrolytes and nonelectrolytes; the size of the molecules involved, and the electric charge of the ions present are of paramount importance. From the research of Friedenwald and co-workers,[4] Duke-Elder and associates[5] and the Boston group, with Cogan, Kinsey, Grant, Jackson and Terry,[6] it would now seem that the old controversy as to whether the aqueous is formed by transfusion or secretion no longer exists. Electrolytes are shown to enter the anterior chamber by secretion, whereas nonelectrolytes enter by ultrafiltration. Moreover, the state of permeability of the semipermeable

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3. Personal communication to the authors.

4. (*a*) Friedenwald, J., and Stiehler, R. D.: Circulation of the Aqueous: VII. A Mechanism of Secretion of the Intraocular Fluid, Arch. Ophth. **20**:761 (Nov.) 1938. (*b*) Friedenwald, J. S.; Buschke, W., and Michel, H. O.: Role of Ascorbic Acid (Vitamin C) in Secretion of Intraocular Fluid, ibid. **29**:535 (April) 1943. (*c*) Friedenwald, J. S.: Dynamic Factors in the Formation and Reabsorption of Aqueous Humor, Brit. J. Ophth. **28**:503, 1944.

5. (*a*) Duke-Elder, S.; Quilliam, J. C., and Davson, H.: Some Observations on the Present Position of Our Knowledge of the Intraocular Fluid. Brit. J. Ophth. **24**:421, 1940. Duke-Elder, S., and Davson, H.: The Significance of the Distribution Ratios of Nonelectrolytes Between Plasma and the Intraocular Fluid, ibid. **27**:432, 1943.

6. (*a*) Kinsey, V. E.; Grant, M., and Cogan, D. G.: Water Movement and the Eye, Arch. Ophth. **27**:242 (Feb.) 1942. (*b*) Kinsey, V. E., and Grant, W. M.: The Secretion-Diffusion Theory of Intraocular Fluid Dynamics, Brit. J. Ophth. **28**:355, 1944. (*c*) Kinsey, V. E.; Jackson, B., and Terry, T. L.: Development of Secretory Function of Ciliary Body in the Rabbit Eye, Arch. Ophth. **34**:415 (Nov.) 1945.

membrane itself, which constitutes the blood-aqueous barrier, influences the exchange through this barrier. The permeability has been demonstrated to be qualitative, inasmuch as it depends on the size of the molecules which are supposed to penetrate it. The factors of simple hydrodynamic pressure and of the state of permeability of the blood-aqueous barrier have not been made sufficiently clear; they must have some influence.

The outflow of fluid from the eye may also be affected by the factors just mentioned, since the exchange through the blood-aqueous barrier may occur in either direction. In addition, there is definite evidence of a flow of fluid entering through the blood-aqueous barrier and leaving through Schlemm's canal. This has become even clearer since Asher[7] demonstrated the merging of the clear aqueous with the epibulbar venous system through the aqueous veins.

For many years, endeavors to solve the problem of regulation of the intraocular tension in glaucoma have been too much dominated by surgical thinking. The more one learns from recent research how subtle and complicated is the problem of the formation and circulation of the aqueous, the more one becomes aware of how clumsy and crude is the procedure of punching holes in the eyeball or coagulating the ciliary body.

The following clinical experiments have emerged from an effort to reverse this attitude of the deification of surgery. They are intended to serve as a contribution to knowledge of how the formation and circulation of the aqueous and the intraocular tension may be influenced by other than surgical procedures and miotics.

Three methods of influencing the intraocular tension were investigated: 1. Action of a particular diet on the composition of the blood and tissue fluids. 2. Reduction of the permeability of the blood-aqueous barrier. Experimental studies on animals concerned with the blood-aqueous barrier were conducted simultaneously by one of us (F.W.S.) and were reported elsewhere.[8] 3. Direct action on the sympathetic and parasympathetic nervous system. This method will be the object of the third study. The present study is concerned with the first method, that of the influence of diet.

INFLUENCE OF RICE DIET ON INTRAOCULAR TENSION

Not much is known about the factor of diet except that the intraocular tension is always lower after meals (Pissarello[9]). Kempner[10] demon-

7. Asher, K. W.: Aqueous Veins: Preliminary Note, Am. J. Ophth. **25**:31, 1942.

8. Stocker, F. W.: Experimental Studies on the Blood-Aqueous Barrier: II. and III., Arch Ophth. **37**:583 (May) 1947.

strated that a diet limited to rice, sugar, fruit and fruit juices, supplemented with vitamins and iron, had a beneficial influence on the course of hypertension on the basis of acute or chronic primary renal disease or of "hypertensive vascular disease." Exclusive of the patients who came in for treatment in such an advanced stage that they died within a short time, hypertension improved in 64 per cent of 167 patients, and the heart became smaller in 91.7 per cent. Of 33 patients with advanced hypertensive retinopathy, the condition became worse in 1, came to a standstill in 11 and improved greatly, or even cleared up completely, in 21. Kempner described his diet as follows:

> The rice-fruit-sugar diet, which, for the sake of brevity, will be referred to as "the rice diet," contains in 2000 calories about 20 Gm. of protein, 5 Gm. of fat, 460 Gm. of carbohydrate, 0.2 Gm. of sodium and 0.15 Gm. of chloride. Patients with marked hypochloremia, or with symptoms of salt deprivation, are given extra sodium chloride in small amounts, or hydrochloric acid. The fluid intake is usually limited to 700-1000 cc. of fruit juices per day (no water).
>
> Dry rice contains about 350 calories per 100 Gm. The average patient can eat 300 Gm., or 10 ounces daily, which will provide about 1050 calories; the remaining 900 or 1000 calories must be supplied by the liberal use of sugar and fresh or preserved fruits. All fruits are allowed, with the exception of nuts, dates, avocados, and any dried or canned fruit, or fruit derivatives, to which substances other than sugar have been added. *No salt is permitted.* All fruit juices are allowed, but tomato or vegetable juices are not. Brown or white sugar may be used *ad libitum.* Any kind of rice is used. The rice is boiled or steamed in plain water or fruit juices, without salt, milk or fat.
>
> The patient should receive daily as minimal doses: Vitamin A, 5000 units; vitamin D, 1000 units; thiamine chloride, 5 mg.; riboflavin, 5 mg.; niacinamide, 25 mg.; calcium pantothenate, 2 mg.; ferrous sulfate, 0.6 Gm.

The effect of such a diet on certain groups of hypertensive patients is unique and has not been attained by any heretofore known low protein, low salt or other diet. A specific factor seems to be connected with the rice, although its existence has not yet been proved to complete satisfaction. Assuming that the intraocular tension is dependent in part not only on the blood pressure but on various factors, including chemical constituents of the blood and tissues, we were interested in investigating the effect which a strict diet of this type might have on the intraocular pressure.

Material.—A group of 20 patients were examined. Three of them had to be excluded from the study because they left the hospital after the first examination and did not return for follow-up study. Three were not on a rice diet and served as controls. Two came in for observation of the intraocular tension only after they

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9. Pissarello, C.: Importanza del rilievo della curva giornaliera di pressione oculare per la diagnosi precoce e per la cura del glaucoma, Ann. di ottal. e clin. ocul. **44**:230, 1915.

10. Kempner, W.: Compensation of Renal Metabolic Dysfunction, North Carolina M. J. **6**:61 and 117, 1945.

had already been on a rice diet. These also served as controls. On 12 patients, we were able to measure the intraocular tension before institution of the rice diet and afterward at regular intervals for an average period of seven and a half weeks. One patient could be followed for only three days. No other period of observation was shorter than ten days. One patient was examined eighteen weeks after the first examination.

Technic.—As long as the patient stayed in the hospital, all measurements of intraocular tension were made in the morning before he had been up, and before he had eaten breakfast. With this routine, the influence of any particular time of the day, of the position of the body and of intake of food was eliminated. Some of the later examinations, after the patient had left the hospital, had to be made at any time of the day, whenever the patient happened to return. All measurements were taken by the same person and with the same Schiötz tonometer.

Readings for Intraocular Tension and Blood Pressure for Subjects 1 *and* 2

Subject	Diet Before (b) and After (a) Rice Diet Was Instituted	Intraocular Pressure, Mm. (Schiotz)		Blood Pressure, Mm. Hg.	
		Right Eye	Left Eye	Systolic	Diastolic
1	9/2/45 (b)	22	25	240	120
	9/5/45 (a)	19	18	200	113
2	1/14/46 (b)	22	22	188	110
	1/25/46 (a)	15	13	184	110

The results of simultaneous measurements of the intraocular and the systolic and diastolic blood pressures are recorded in the table and in charts 1 to 5.

In the 12 patients who remained after elimination of the 8 patients, a striking reduction in intraocular pressure was observed as soon as the rice diet was instituted. The degree of reduction varied from patient to patient and during the course of the treatment, but reductions of 5 to 7 mm., persisting over long periods, were not uncommon. In most patients a parallel decrease in the systolic and diastolic blood pressures was observed. It was possible, therefore, that the reduction in intraocular pressure was simply the result of the reduction in arterial pressure. However, there was no definite parallelism between the decrease in tension in the two systems. Some patients who responded with a sharp lowering of blood pressure had only moderately reduced intraocular pressure,[11] and patients with relatively poor response of the blood pressure showed a considerably lower intraocular pressure.[12] The two groups of controls also gave interesting information as to the relation of intraocular tension and blood pressure. Patients who were not given a rice diet did not show an equally great reduction of intraocular

11. Kinsey and others.[6a] Asher.[7]

12. Hess and Lehmann.[2b] Friedenwald and Stiehler.[4a] Friedenwald, Buschke and Michel.[4b]

tension, even if the blood pressure was reduced by other measures[13]; nor did the patients who had been given a rice diet before the intraocular tension was taken show any additional reduction when further measure-

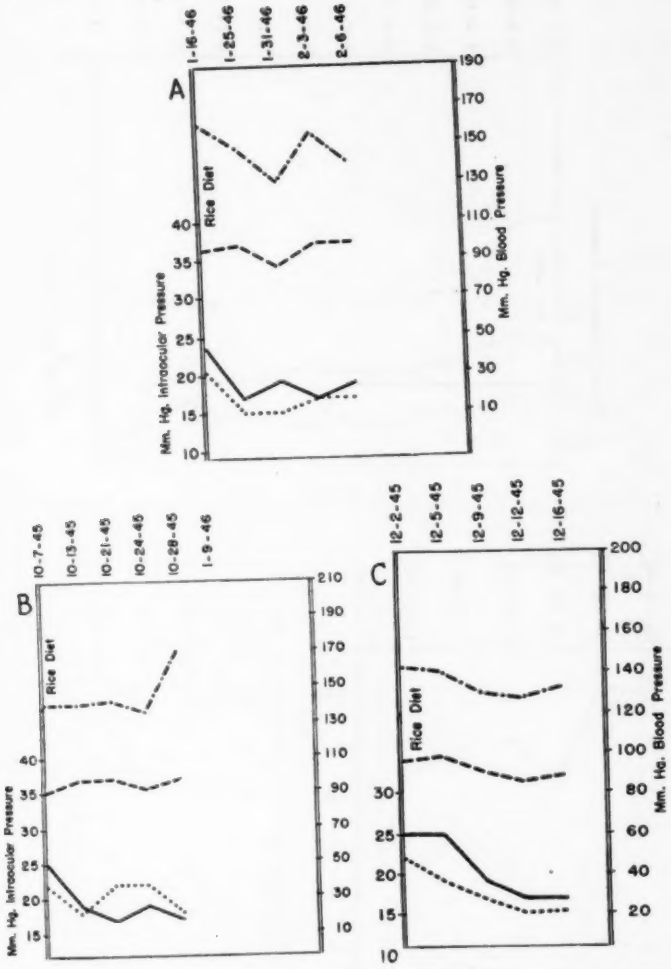

Chart 1 (subjects 3 to 5).—Relation of intraocular pressure to blood pressure.

In this chart, and charts 3 to 5, the line of dots and dashes indicates the systolic blood pressure; the line of dashes, the diastolic blood pressure; the solid line, the intraocular tension in the right eye, and the line of dots, the intraocular tension in the left eye.

ments were made. The striking irregularity in both intraocular tension and blood pressure in patient 8 might be explained on the basis that this patient was highly nervous and excitable.

13. Stocker.[8] Pissarello.[9]

These facts, indeed, point to the conclusion that it cannot be merely the decrease in blood pressure that influences the intraocular tension;

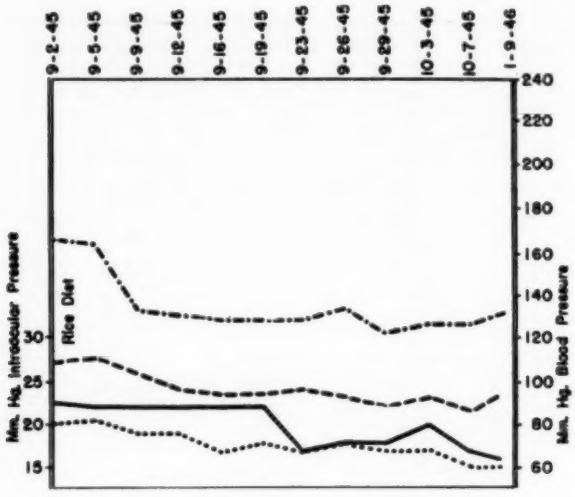

Chart 2 (subject 6).—Relation of intraocular tension to blood pressure.

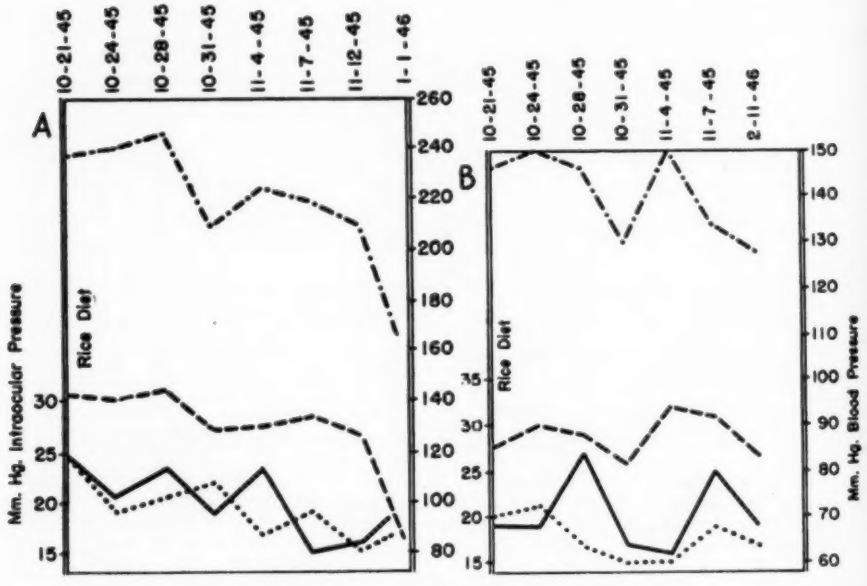

Chart 3 (subjects 7 and 8).—Relation of intraocular tension to blood pressure.

rather, there must be some specific effect of the rice diet. What may be the factor that produces this remarkable decrease in intraocular tension?

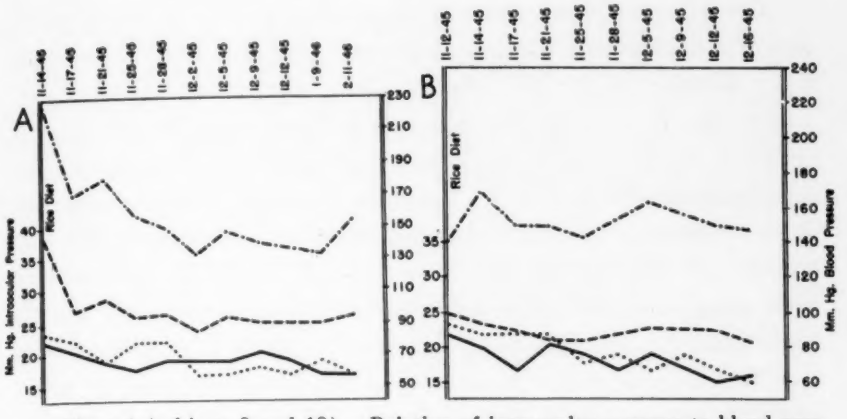

Chart 4 (subjects 9 and 10).—Relation of intraocular pressure to blood pressure.

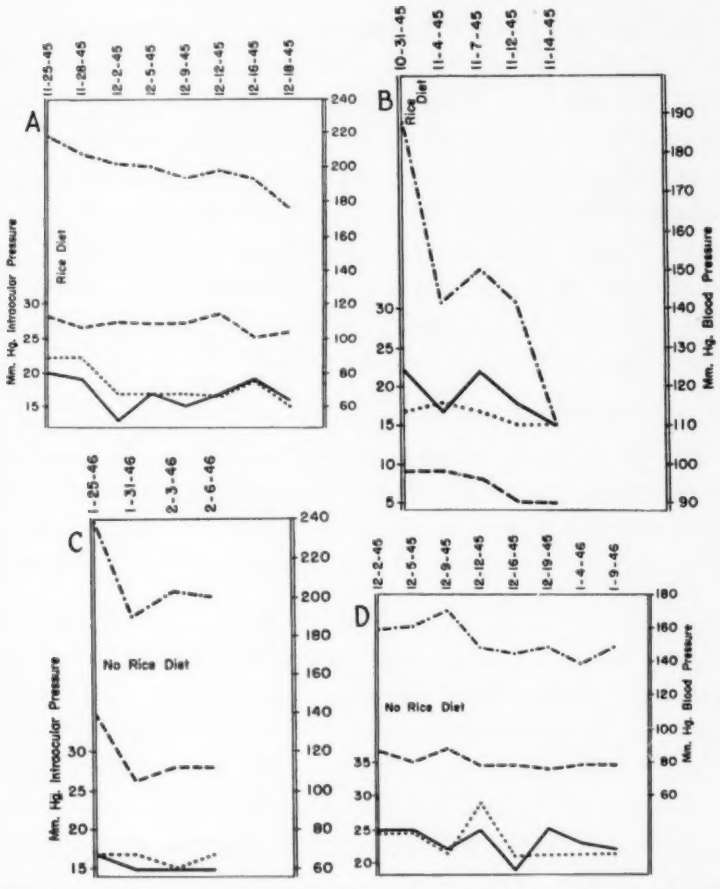

Chart 5 (subjects 11-14).—Relation of intraocular tension to blood pressure.

The influence of the rice diet on metabolism and the blood chemistry was extensively studied by Kempner. Here are some of the main facts: In spite of the low protein intake, the protein equilibrium of patients on the rice diet was maintained. Striking was the decrease in excretion of chlorides in the urine. In a typical case urine chlorides which had measured 83 and 73 milliequivalents while the patient was given a regular hospital diet decreased to 47 milliequivalents after only two days of rice diet and were found to be 2.7 and 3.2 milliequivalents after twenty-one and twenty-six days of rice diet, respectively. On the other hand, the reduction of plasma chlorides did not reach the critical level. Average values for 91 patients were 97.0 milliequivalents before and 91.7 milliequivalents after an average of forty-four days of rice diet.

The explanation of the phenomenon of the reduction in intraocular tension by the rice diet is still hypothetic. For a time we thought that a relative depletion in chlorides of the tissues brought about by the low chloride rice diet might have something to do with it. But recently we are more inclined to attribute the drop in tension to a possible reduction in the secretion of sodium by the ciliary body. This would be in line with the changes taking place in the kidney. There the process is one not of secretion, but of reabsorption of sodium in the tubules, which is diminished after the use of the rice diet. But, whatever the explanation may be, the fact exists that in certain circumstances the intraocular tension may be influenced by dietary measures.

The rice diet is essentially a low protein, low chloride and low sodium diet. Whether a specific factor, pertaining to the rice as such, contributes to the spectacular results in certain cases of arterial hypertension has not yet been ascertained. For the explanation of the reduction of the intraocular tension, the assumption of such a factor does not seem necessary.

The group of patients who showed such a remarkable decrease in intraocular tension after they had been given a strict rice diet had arterial hypertension. They showed various degrees of hypertensive alterations in the eyeground, but none of them had glaucoma. From the standpoint of intraocular tension, they were to be considered normal. How glaucomatous patients will react to the same diet will be demonstrated by another series of experiments and reported on completion of the study.

SUMMARY

The influence of the "rice diet," as introduced by Kempner for the treatment of hypertensive vascular disease, on the intraocular tension of nonglaucomatous patients was studied. All patients subject to this diet showed a striking and persistent reduction of intraocular tension. The reduction of the intraocular tension did not seem to be directly dependent on the reduction of the blood pressure. It is believed that a relative depletion of chlorine and sodium ions in the body tissues, including the eye, might be the underlying factor in this phenomenon.

1110 West Main Street.

TUMORS OF THE OPTIC NERVE

Long Survival in Three Cases of Intracranial Tumor

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THE OPTIC nerve, by virtue of its anatomic position, acts as a pathway for disease within the orbit, on the one hand, and disease within the cranium, on the other. Because of this fact, it is not surprising that the interdependence of ophthalmologists and neurosurgeons with regard to certain problems concerning tumors of the optic nerve continues to exist. A discussion of some aspects of these tumors will serve to illustrate this relationship.

The earlier communications concerning tumors of the optic nerve were confined almost solely to their intraorbital manifestations. The characteristic history of a child with progressive loss of vision in one or both eyes together with painless unilateral proptosis was in itself suggestive of an intraorbital tumor of the optic nerve. With the development of neurosurgery, the region of the optic chiasm became exposed with greater frequency and safety. Craniotomy performed in search of an intrasellar or a suprasellar lesion disclosed on rare occasions a tumor of the chiasm or of the optic nerve itself. The diagnosis of neoplasms in the latter site is based on evidence subtler than that presented by their orbital counterpart, but it is well to remember that tumors of the optic nerve, whether along its intracranial portion or within the orbit, are in fact the same disease.

Scarpa,[1] in 1816, made notes about a patient with an orbital tumor which seemed to take its origin from the sheath of the optic nerve. There is little question, however, that Wishart,[2] in 1833, was the first

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1. Scarpa, cited by Byers;[3] cited by Demarquay: Traité des tumerus de l'orbite, Paris, V. Masson, 1860.

2. Wishart: A Case of Extirpation of the Eyeball, Edinburgh M. & S. J. **40**:274, 1833.

to describe the lesion clearly. Some excerpts from his case report are of unusual interest and are presented here:

> Euretta Douglas, age 13. On her looking downwards with the eye a firm tumor can be distinctly felt near the situation of the lacrymal gland. . . . For the first three months nothing was done for it; but after that there was such a rapid increase in size that the surgeon who was consulted pronounced it to be dropsy of the eye. He applied leeches over the eyebrow and blisters to the temple without producing any mitigation of the symptoms. . . . At a consultation with Dr. Gillespie and Prof. Lizars it was agreed that nothing could be done to save the eye. . . . I removed the eye, assisted by the gentlemen and Mr. Burt on the first of March.
>
> On examination of the eye after its removal the disease was found to be seated in the substance of the optic nerve; the coat of the nerve being very much distended and evidently forming the outer cover of the tumor. . . . The tumor was of a firm consistency resembling cerebral substance, generally considered of a malignant nature. I have never met with any cases of the same description (as this) in the works of surgery or morbid anatomy which I have examined. The only one resembling it is related by Panizza in his work "Sul Fungo Midollare" in a little girl six years of age in which there was found on dissection not only a small tumor surrounding each optic nerve but a still larger cerebral mass at the base of the brain.

The tumor described here by Wishart was undoubtedly a glioma of the optic nerve. As will be pointed out later, this type of tumor should be classified as an intraneural tumor of this structure.

In Wishart's reference to the patient of Panizza, it is fairly clear that the tumor described originated intracranially and extended into the orbit. Extension from the orbit to the intracranial cavity is, however, perhaps more frequent. In 191 cases of tumor of the optic nerve studied independently by Byers[3] and Hudson,[4] evidence of definite intracranial involvement was presented in 40 (21 per cent). This percentage must, of course, be considerably higher, since the terminal events in the lives of most of the patients are not known. In only 8 of Byers' 112 cases was the patient known to have remained well for more than five years. In a collective survey of the cases reported by Byers and by Hudson, 23 postmortem examinations were noted. Of these, 21 revealed intracranial extension. Fourteen of the 21 necropsies were performed on patients who died of postoperative meningitis, and it should be noted that these 14 patients had intracranial spread of the tumor at the time of the treatment of the orbital tumor.

From all this, it can be appreciated that a tumor of the optic nerve, whether intraorbital or intracranial, represents a single lesion possessing at least the potentiality of spreading from the orbit to the chiasmal

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3. Byers, W. G. M.: Primary Intradural Tumors of the Optic Nerve: Fibromatosis Nervi Optici, Stud. Roy. Victoria Hosp., Montreal **1**:3-82, 1901.

4. Hudson, A. C.: Primary Tumors of the Optic Nerve, Proc. Roy. London Ophth. Hosp. Rep. **18**:317-439, 1912.

region or in the opposite direction. On the other hand, Byers,[3] in 1901, wrote:

> . . . when a primary tumor of the optic nerve causes death it is, I believe, never because of a spreading backward of the orbital tumor but through the continued growth of an intracranial portion of the neoplasm which coexists with the orbital tumor and which is not removed at the time of operation. . . . It may be that the removal of the orbital portion [of the tumor] may in some way retard or stop the growth within the skull . . . but it is highly probable that in the majority of these cases the unexcised cerebral (tumor) continues on its course of development and sooner or later brings about the death of the patient.

The description of the types of tumors of the optic nerve remained in a chaotic state until Hudson,[4] in 1911, brought order to the subject in his classic paper. He designated three types of tumors, namely, the neoplasms characterized by gliomatosis (gliomas), the endotheliomas and the tumors characterized by fibromatosis of the nerve sheath (fibromas). In a comprehensive review of the clinical and pathologic aspects of tumors of the optic nerve, Davis[5] stated that most authors are now agreed to the general classification given by Hudson. Davis reviewed 305 cases reported up to 1934 and tabulated them as follows:

Gliomatosis (glioma)	193	(probable and certain)
Endotheliomas	86	(probable and certain)
Fibromatosis of the sheath	8	
Diagnosis uncertain	18	
	305	

The classification of tumors of the optic nerve was further simplified by Verhoeff,[6] who divided them into two general groups: (1) intraneural tumors of the optic nerve, namely, the gliomas arising within the nerve stem; and (2) extraneural tumors of the optic nerve, arising in the nerve sheath and comparable to the meningiomas of the brain. Verhoeff's classification, aside from its simplicity, has still another virtue. It recognizes the embryologic and histologic characteristics which make the second nerve unique. Wolff[7] expressed the situation well in these words:

> The optic nerve is no nerve at all but part of the brain and its tumors will be in all essential features identical with those of the brain; and just as there is only one brain tumor, the glioma, so there is only one intraneural tumor of the optic nerve, also the glioma.

The extraneural tumors of the brain and optic nerve arise from the meninges. These tumors (meningiomas or endotheliomas) characteristi-

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5. Davis, F. A.: Primary Tumors of the Optic Nerve (Phenomenon of von Recklinghausen's Disease): A Clinical and Pathologic Study with a Report of Five Cases and a Review of the Literature, Arch. Ophth. **23**:735-821 (April); 957-1022 (May) 1940.

6. Verhoeff, F. H.: Primary Intraneural Tumors (Gliomas) of the Optic Nerve, Arch. Ophth. **51**:120-140 (March); 239-254 (April) 1922.

7. Wolff, E.: Discussion on Tumors of the Optic Nerve, Proc. Roy. Soc. Med. **33**:685-692, 1940.

cally compress and indent the underlying nerve elements but do not invade nerve structures.

Until 1911, when Hudson published his review of the tumors of the optic nerve, there were less than 350 reported cases. The ratio of intraneural to extraneural growths was 3:1. Both types were commoner in the female. The age of onset of symptoms in patients with tumors of these two types is especially noteworthy. Of the 118 cases of intranueral tumors summarized by Hudson, symptoms were presented in the first ten years of life in 75 per cent and in the first five years in 40 per cent. There were 29 cases of extraneural tumors in Hudson's review. Of these, the onset of symptoms was in the first decade of life in only 10 per cent, while in 50 per cent symptoms first developed after the thirtieth year.

According to Verhoeff, the high percentage of cases of intraneural tumors in which symptoms develop early in life "suggests they are congenital in origin and due to some more or less localized abnormality of embryonic development of neuroglia of the nerves." More than 50 per cent of the patients with extraneural tumors of the optic nerve begin to show symptoms after the thirtieth year. This type of tumor of the optic nerve is said to cause intracranial involvement about as frequently as does the intraneural type.

Although intraneural tumors (gliomas) tend to grow backward toward the brain, an extension forward sometimes occurs. Case 1 in the series reported by Verhoeff was the only one described up to that time in which the tumor spread distally to involve the globe. Other cases of spread of tumor tissue into the nerve head have since been reported; our case 3 is a probable instance of distal spread.

The intraneural tumor or glioma of the optic nerve spreads by direct extension. The mechanism of this spread has been studied in great detail. The theory expressed by Councilman[8] is perhaps the most plausible. He stated:

> Advance of the tumor is preceded by general proliferation of the neuroglia cells which become converted into cells of the tumor and have the growth and form characteristic of these. It is impossible to avoid the impression that in the tumor or in some way associated with it a substance is produced which stimulates the neuroglia to growth. This growth takes the form of both general gliosis and of tumor. . . . The only changes which take place in the ganglion cells are those of atrophy and degeneration. They never take part in the formation of the tumor.

The good results which have been achieved by incomplete removal of the intraorbital gliomas of the optic nerve lend credence to this theory. Verhoeff noted that "removal of the largest part of the tumor may do away with the assumed stimulating substance and thus prevent

8. Councilman, W. T.: Anatomical Considerations of Tumors of the Brain with Special Reference to the Gliomata, Colorado Med. **12**:289, 1915.

further extension of the growth." In Hudson's review of 118 cases of intraneural tumors it can be seen that after incomplete removal of the intraorbital lesion local recurrence was rare.

The diagnosis of tumors of the optic nerve is not difficult when the neoplasm is confined to the orbit. Both the intraneural and the extraneural orbital growths cause unilateral exophthalmos, followed by progressive amaurosis. The impairment in vision sometimes precedes the proptosis in cases of intraneural tumor. The exophthalmos is usually

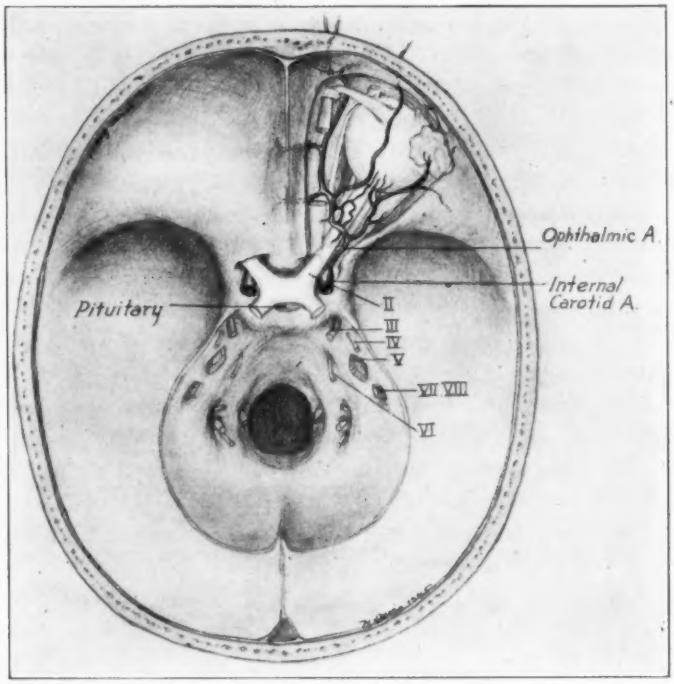

Fig. 1.—Sketch showing the general relationship of the optic nerves and chiasm of the sella turcica, the internal carotid arteries and neighboring cranial nerves (adapted from Spalteholz "Handatlas der Anatomie des Menschen" and "Gray's Anatomy").

painless. Pain in and limitation of movement of the eyeball are more commonly observed in patients with extraneural tumors.

In the event that a tumor of the optic nerve is confined to or spreads along the intracranial portion of the nerve, the diagnosis becomes somewhat more difficult. The clinical symptoms often simulate those of other tumors in the suprasellar or chiasmal region. The common features include primary atrophy of the optic nerve, changes in the visual fields and a deformed or enlarged sella. In addition, there may be suprasellar shadows, oculomotor palsy, diabetes insipidus, som-

nolence, obesity and secondary disturbances of the pituitary gland. The likelihood of such symptoms is evident if one bears in mind the relation of the optic nerves and chiasm to the neighboring structures (fig. 1). Dandy[9] expressed the belief that one should always think of a tumor of the optic nerve in any case of unexplained blindness. Roentgenographic evidence of an enlarged optic foramen or erosion under the anterior clinoid process is significant. This point was brought out by Martin and Cushing[10] and was also emphasized by van der Hoeve.[11] In cases in which symptoms point to the suprasellar region and no suprasellar shadow can be demonstrated in the roentgenogram the possibility of a tumor of the optic nerve should be borne in mind.

The detection of an enlarged sella turcica, bitemporal hemianopsia and primary optic nerve atrophy with evidence of pituitary deficiency would usually indicate an adenoma of the pituitary gland. However, these manifestations can be simulated to some degree by a tumor of the optic nerve, although as a rule the differentiation is not difficult. Actually, tumors of the optic nerve have for the most part been disclosed when the chiasmal region was explored with the expectation of finding a suprasellar lesion, such as a craniopharyngioma or a meningioma of the tuberculum sellae.[12]

Of the 345 verified intracranial gliomas of all kinds reported by Martin and Cushing[10] in 1923, 7, or 2 per cent, were chiasmal, and this number represented 0.84 per cent of all the 826 verified intracranial tumors in Cushing's series at that time. The relative frequency of these growths as they occur in the region of the sella was noted by Heuer.[13] In his review of 37 cases of chiasmal lesions, 73 per cent of the tumors were hypophysial, 24.3 per cent suprasellar and 2.7 per cent chiasmal.

It is obvious that the intrasellar tumors, by virtue of their somewhat more clearly defined clinical manifestations and their numerical preponderance, are more suspectible to accurate diagnosis than are the suprasellar growths, including tumors of the optic nerve, and that the differential diagnosis of a tumor in this region, either suprasellar or

9. Dandy, W. E.: Prechiasmal Intracranial Tumors of the Optic Nerves, Am. J. Ophth. **5**:169-188, 1922.

10. Martin, P., and Cushing, H.: Primary Gliomas of the Optic Chiasm and Optic Nerves in Their Intracranial Portion, Arch. Ophth. **52**:209-241 (May) 1923.

11. van der Hoeve, J.: Roentgenphotographie des Foramen opticum bei Geschwülsten und Erkrankungen des Sehnerven, Arch. f. Ophth. **115**:335-369, 1925.

12. Other lesions in the sellar region which on rare occasions may produce a similar clinical picture are gliomas of the infundibulum; parasellar, infrasellar and suprasellar aneurysms; an anomalous ophthalmic artery, and chiasmal arachnoiditis (either syphilitic or post-traumatic).

13. Heuer, G. J.: Surgical Experiences with an Intracranial Approach to Chiasmal Lesions, Arch. Surg. **1**:368-381 (Sept.) 1920.

intrasellar, is as a rule not difficult. On the other hand, the differentiation of certain craniopharyngiomas from tumors of the optic chiasm at times cannot be made with certainty. The accompanying tible, adapted from Martin and Cushing,[10] is helpful in distinguishing between tumors of these types.

Ophthalmologists have been acquainted with tumors of the optic nerve for a longer period than have neurosurgeons. From the former's experience with the intraorbital portion of these growths, there developed the impression that tumors of the optic nerve were slow growing and that further growth of the neoplasm could be prevented or further diminished by incomplete removal of the lesion. For a time the prognosis of these tumors seemed hopeful. Byers, however, was among the first to realize that the disease was a serious one and that the real danger

*Differentiation of Suprasellar and Intrasellar Tumors**

Tumor or Craniopharyngeal Pouch	Tumor of Chiasm
Primary optic nerve atrophy, with edema superimposed in late stages, owing to hydrocephalus	Primary optic nerve atrophy; superimposed papilledema if intracranial pressure is increased; rarely, involvement of nerve head by tumor; exophthalmos with intraorbital spread of tumor
Bitemporal hemianopsia; if vision lost in one eye, fairly acute vision retained in seeing half of other	Acuity low in both eyes, with fields showing less typical hemianoptic defects
Progress slow, often stationary for years	Progress on the whole more rapid and progressive
Sella variously deformed, enlarged or normal; posterior clinoid process more affected than anterior; suprasellar shadows common	In advanced stages, apparent extension of sella under anterior clinoid processes due to distention of optic foramens; no suprasellar shadows
Secondary manifestations of pituitary dysfunction common, with adiposogenital dystrophy and infantilism	Secondary manifestations of pituitary dysfunction inconspicuous; cutaneous indications of Recklinghausen's disease to be looked for

*Adapted from the table of Martin and Cushing.[10]

was concerned with the spread of the tumor along the intracranial portion of the optic nerve. An intraorbital tumor of the optic nerve, in spite of the dramatic exophthalmos and amaurosis which it produces, does not endanger the life of the patient as does the less obvious intracranial tumor of this structure.

Evidence of the extremely poor prognosis of tumors of the intracranial portion of the optic nerve was presented by Martin and Cushing in their summary of the 7 cases of verified gliomas of the chiasmal region to which reference has been made. Three of their patients died after operation, of hyperthermia; 1 patient died six months after removal of a portion of the tumor along with the right optic nerve, and 2 patients died one year after operation. The seventh patient survived the exploratory operation for an unreported period. Such uniformly

unfavorable results following the operative treatment of these tumors led Martin and Cushing to write:

> Unquestionably, if we may come in time to perfect our clinical diagnosis of these lesions, there is every reason to avoid operating upon them, though in cases of doubt an exploration may have to be made.

From our experience with the cases about to be reported, it would seem that such a pessimistic attitude is unwarranted. A more hopeful

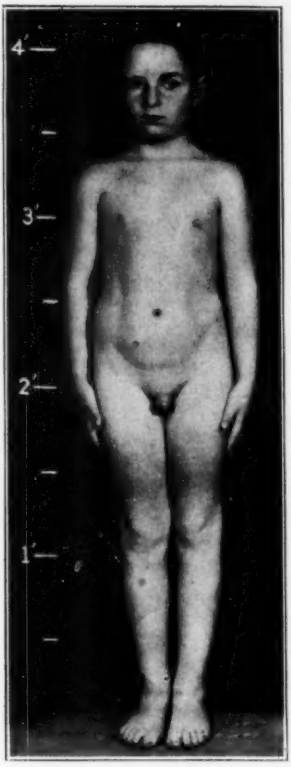

Fig. 2 (case 1).—Appearance before operation, showing slight secondary manifestations of hypopituitarism, a tendency to obesity and infantile genitalia.

note, likewise, has been sounded recently by Jackson,[14] who reported the removal of an intracranial glioma in a child 4½ years old. The patient was in perfect health eight and one-half years after the operation. Likewise, in this communication, Jackson gave an excellent summary of the symptoms, diagnosis and treatment of orbital tumors.

REPORT OF PERSONAL CASES

Since 1932, 3 patients with intracranial tumors of the optic nerve have been treated by one of us (G.H.) at the Lahey Clinic. For reasons

14. Jackson, H.: Orbital Tumours, Proc. Roy. Soc. Med. **38**:587-594, 1945.

not apparent to us, all these patients have remained in remarkably good health over a period of years. It is now over twelve years since W.A. (case 1) was operated on and the diagnosis established histologically. This young man was in the Army of the United States in Germany and has recently returned home. M.H. (case 2) has been in good general health for over ten years after her craniotomy. The third patient (M.O'B.) was in excellent health at her last report, four and one-half years after operation.

The long periods of survival, in apparent good health, of these patients is noteworthy not only for its own sake but also in reevaluation of the prognosis of intracranial tumors of the optic nerve.

Case 1.—W. A., an 8 year old boy, was seen at the Lahey Clinic on Jan. 22, 1934, having been referred by Dr. J. J. Skirball, of Boston. He was admitted to

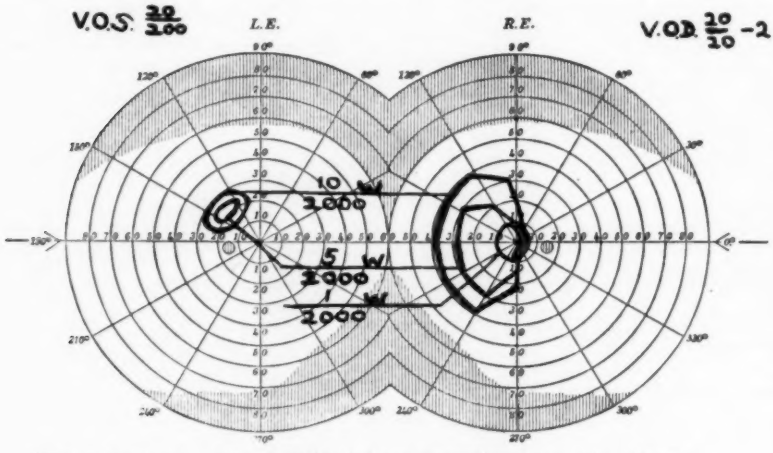

Fig. 3 (case 1).—Visual fields before operation (Jan. 22, 1934).

the New England Deaconess Hospital on the same date. The patient complained of failing vision in the left eye for the past year. During the preceding six months the left eye on occasion had turned in. One year earlier the school authorities notified the parents that the patient's vision was not up to standard, although it had previously been normal. Eye glasses were advised by the local physician. The left eye occasionally became inflamed and burned for the few months before his visit here. There was no diplopia. The patient was able to read well, but his mother thought that the vision was becoming progressively worse.

Examination revealed that the pupils were round, regular and equal and reacted to light and in accommodation. Extraocular movements were normal except for a few nystagmoid jerks to the right and left. The right fundus revealed moderate atrophy of the optic nerve; the optic cup was present, with slight engorgement of the veins. The left fundus presented a picture of advanced atrophy of the optic nerve; the optic cup was present, and the veins were greatly engorged. The sense of smell was intact bilaterally. The patient was inclined to obesity. He had hairless skin and infantile genitalia (fig. 2). Visual acuity was 20/20—2 in the right eye and 20/200 in the left eye. The visual fields before operation disclosed

temporal hemianopsia in the right eye and almost complete blindness in the left (fig. 3). Roentgenograms of the skull had been taken elsewhere, and the following report was sent to us: "There are definite erosion and depression of the anterior portion of the sphenoid bone at the edge of the sella in the region of the sulcus chiasmaticus. With this there are deep, hollowed-out areas under each anterior clinoid process, extending forward to the optic foramens. This is the appearance usually seen with gliomas of the optic chiasm (fig. 4) . . . The lesion in this case is inoperable as there is diffuse involvement of both nerves. The prognosis is eventually complete blindness. The only hope is that my diagnosis is incorrect."

In spite of this definite diagnosis from an expert roentgenologist, it was felt that the chiasmal region should be explored, in the hope that the lesion was of some other type.

Operation.—On Jan. 23, 1934, with the patient under anesthesia induced with solution of tribromoethanol U.S.P. and ether, right transfrontal craniotomy

Fig. 4 (case 1).—Roentgenogram of the sella turcica, showing hollowed-out areas under the anterior clinoid processes and displacement backward of the dorsum sellae.

was performed (G.H.). The dura was under increased tension and was opened. The right frontal lobe was retracted, revealing a suprasellar tumor, which was grayish red, soft and probably cystic. The impression at this stage in the operation was that the tumor was a cyst of Rathke's pouch. A needle was inserted, but no fluid could be aspirated. The right optic nerve was observed to be pushed laterally by the growth. The tumor capsule was cauterized and excised. Tumor tissue was removed with the pituitary spoon, and the tissue was noted grossly to resemble adenoma of the pituitary gland. A radical intracapsular evacuation of the growth was accomplished. The right optic nerve was thereby relieved of the pressure which was

stretching it, and this nerve settled back into its normal position with collapse of the capsule beneath it.[15]

Pathologic Report.—Sections stained with hematoxylin and eosin showed tissue composed almost entirely of astrocytes, which were greatly increased in number, atypical in pattern and with some variation in the configuration of nuclear form. In some foci these neoplastic astrocytes were condensed around an increased number of vascular channels, and they had a pronounced fibrillary pattern. This was brought out with a special stain, the glial fibrils forming a fairly dense meshwork.

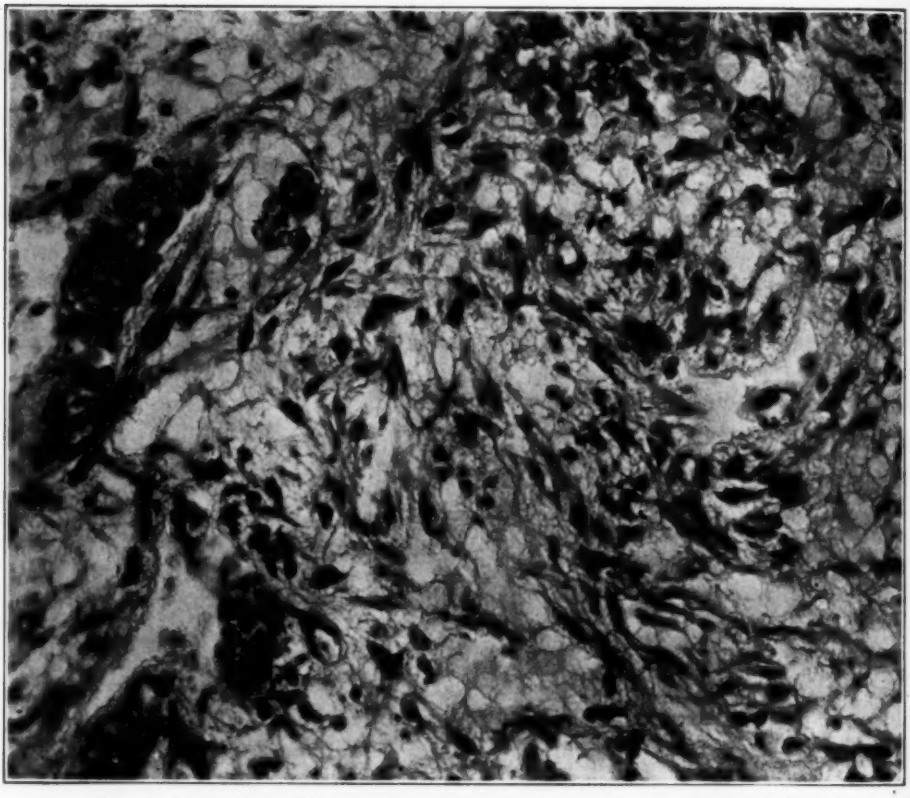

Fig. 5 (case 1).—Microscopic appearance of tumor, composed of fibrillary astrocytes. × 350.

The diagnosis was fibrillary astrocytoma (fig. 5).

Postoperative Course.—The patient had an uneventful convalescence and noted some improvement of vision in the left eye. He was given four roentgen treatments in March 1934. He returned to school in September 1934 and achieved

15. It is interesting that in the operative note made by one of us (G.H.) it is stated that the left optic nerve was never visualized. It is probable that what was taken to be the tumor medial to the right nerve was actually the tumor incorporated in the substance of the left nerve and that the exit of the nerve from the skull could not be seen.

better grades than before operation. He returned yearly for examination, each time stating that the left eye had a tendency to turn inward after exercise and fatigue. His general health remained excellent, and he participated in active sports. At the age of 12½ years, pubic hair developed and the genitalia were normal, but there was no axillary hair. The right optic disk looked almost normal, but the left continued to show advanced primary atrophy of the optic nerve. The patient was seen in October 1940, at which time he was in good general condition, without complaints. Visual acuity and visual fields had remained almost exactly as they were before operation, and as taken four years after operation (fig. 6). A letter from the patient's mother, dated June 28, 1946, stated that the patient had been in the Army in Europe for a year and was in excellent health, awaiting transportation home. She enclosed a recent snapshot of the patient (fig. 7).

The patient himself returned to this country and reported for a personal check-up on Dec. 3, 1946. He was looking the picture of health (fig. 8). Subjectively and objectively, his vision had remained unchanged from that in the previous examinations.

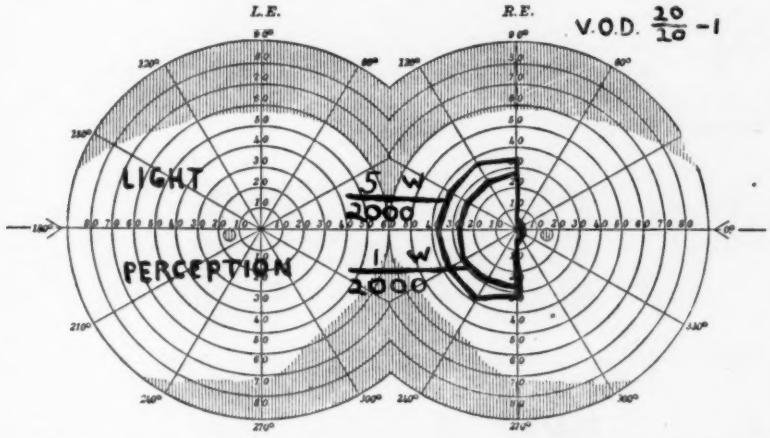

Fig. 6 (case 1).—Visual fields four years and ten months after operation (Nov. 25, 1938). These have remained unchanged up to the present time, twelve years after operation.

Comment.—The extraordinary story of this patient speaks for itself. His clinical picture and the gross appearance of the growth at the time of operation were so typical of a pituitary tumor (either adenoma or craniopharyngioma) that the eventual pathologic report came as a complete surprise. It is of considerable interest that the roentgenologist was able to make the correct diagnosis, but it is likewise fortunate that his advice as to the inoperability of the growth was not followed. How this patient could have been inducted into the Army, in view of his extremely limited vision, must remain a mystery.

It is now twelve years since the operation, and there is still no evidence that the tumor has extended or recurred. It is barely possible that the high voltage roentgen therapy which was given after opera-

tion may have had an inhibitory influence on the growth; although this is unlikely in cases of fibrillary astrocytoma, Dyke and Davidoff[16] expressed the belief that such treatment is helpful.

Case 2.—M. H., a white married woman aged 52, was seen at the Lahey Clinic on Sept. 30, 1936, having been referred by Dr. William Allen, of Unadilla,

Fig. 7 (case 1).—Snapshot of patient while in the Army of the United States in Europe (1946), twelve years after operation.

Fig. 8 (case 1).—Appearance of patient at last report, in December 1946.

Fig. 9 (case 2).—Appearance of patient before operation showing slight exophthalmos on the left.

N. Y., and on this date was admitted to the New England Deaconess Hospital. The patient's chief complaint was blindness in the left eye for one year. She recalled that she had always needed stronger glasses on the left side, but that four or five years prior to admission she had noted failing vision of the left eye.

16. Dyke, C. G., and Davidoff, L. M.: Roentgen Treatment of Diseases of the Nervous System, Philadelphia, Lea & Febiger, 1942.

This had progressed until one year ago she was completely blind in the left eye. She recalled that the left temporal field disappeared first.

Physical examination revealed exophthalmos on the left side (fig. 9). With a base line of 109, readings of the exophthalmometer were 22 mm. for the left eye and 12 mm. for the right eye. The left pupil was larger than the right and reacted only in accommodation, but not to light. Extraocular movements were normal. The fundi revealed slight pallor of the right optic disk, with extreme pallor of the left. The veins were tortuous bilaterally. The remainder of the neurologic examination revealed nothing significant. Although the patient was completely blind in the left eye, the visual acuity and visual field of the right eye were normal (fig. 10).

Roentgenograms of the skull revealed a faint area of calcification above and anterior to the sella in the midline. In addition, the anterior clinoid processes were separated more than usual, and there was atrophy of the posterior clinoid process. These changes suggested a suprasellar tumor.

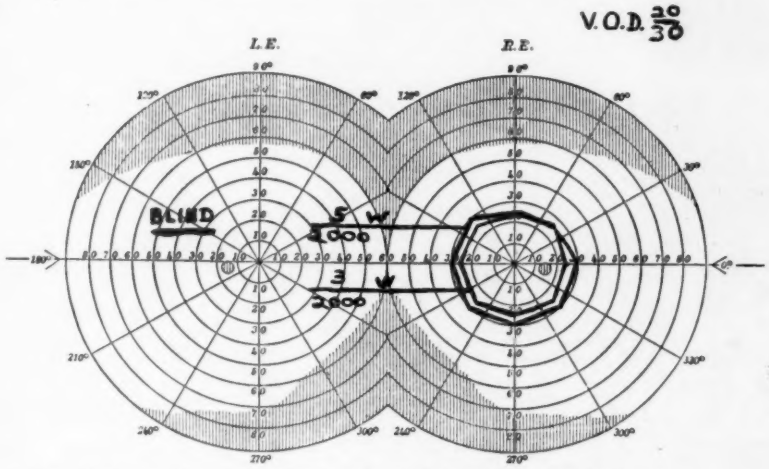

Fig. 10 (case 2).—Preoperative visual fields (Oct. 4, 1936).

Operation (Oct. 5, 1936).—A left frontal craniotomy was performed by one of us (G.H.). When the orbital plate was exposed, it was seen to be exceedingly thin, and it was therefore felt that an intraorbital tumor was present. The orbital plate was therefore removed and the capsule surrounding the orbital contents incised. This procedure permitted the structures within the orbit to bulge backward, with the release of high intraorbital pressure.

The frontal lobe was now retracted, and an unusual bulge in the region of the left optic nerve was disclosed. In order to secure satisfactory exposure, a portion of the tip of the left frontal lobe was excised. It was then possible to see that a tumor about the size of an English walnut was incorporated within the substance of the left optic nerve. It was grayish yellow, and its capsule was continuous with the sheath of the nerve.

The surface of the tumor was coagulated and then incised, after which the growth was removed piecemeal from within the capsule with the use of pituitary rongeurs, as well as by sharp dissection with knife and scissors, because of its fibrous nature. The growth apparently extended backward well into the left side of the optic chiasm, so that the removal was regarded as incomplete. The optic

foramen was completely decompressed, in addition to removing the orbital plate, as already noted.

Postoperative Course.—The patient made a good convalescence, and at the time of her discharge, on October 24, her physical status showed no essential change from that before operation. Her left eyeball had perhaps receded slightly (1 to 2 mm. on the exophthalmometer).

Pathologic Report.—Microscopic sections showed chiefly fibrosis. The tissue was composed chiefly of fibrocytes and narrow, interlacing bands of collagen.

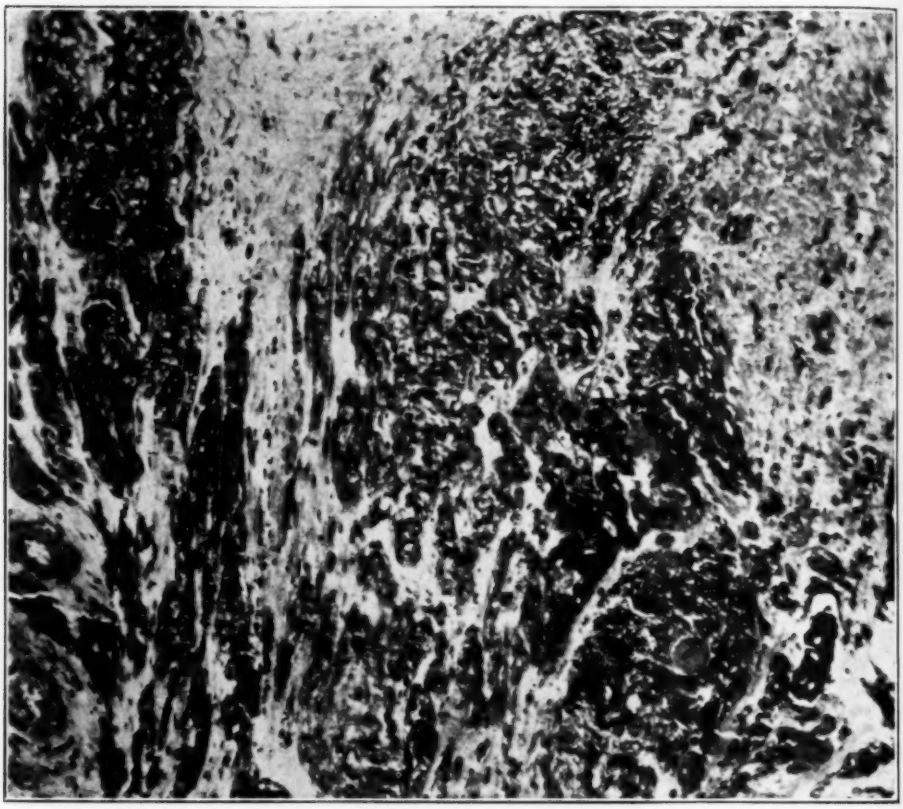

Fig. 11 (case 2).—Photomicrograph of tumor, showing its general fibrous character, together with areas of degeneration and obliterative endarteritis; × 110.

While the fibrous tissue was not actively proliferating, much appeared to have been laid down recently. There were frequent irregular areas of partial tissue degeneration, some suggesting degenerated nerve tissue; in one of the areas there was a small focus of calcification. A scattering of hemosiderin was present throughout the tissue. Although there were few vessels of arteriolar size or larger, those that could be identified showed obliterative endarteritis, often to the point of complete occlusion. About some of these vessels was a cuff of lymphocytes with some polymorphonuclear neutrophils. An occasional venule also showed this perivascular cuffing. There were no mitotic figures, atypical cell or nuclear forms or other indications of neoplastic or rapid growth (fig. 11).

On June 28, 1944, the patient had a Miles resection for adenocarcinoma of the rectum and was in good health otherwise when she was discharged from the hospital after this operation, on Aug. 1, 1944, seven years and eight months after the tumor of the optic nerve had been removed. Her vision had remained the same as that before her intracranial operation. A letter from the patient, dated Jan. 13, 1947, ten years and four months after operation, stated that the sight of her right eye was as good as ever.

Comment.—From the clinical and neurologic standpoints, this woman had the symptoms of a retro-orbital tumor, such as a meningioma of the sphenoidal ridge, or possibly an aneurysm. The roentgenologic findings, however, did not support the evidence of a tumor of the sphenoidal ridge, but, rather, were in favor of a suprasellar growth because of the calcification above the sella. Again, the long period of survival (ten years and four months) is most encouraging, especially in view of the obviously incomplete removal of the tumor.

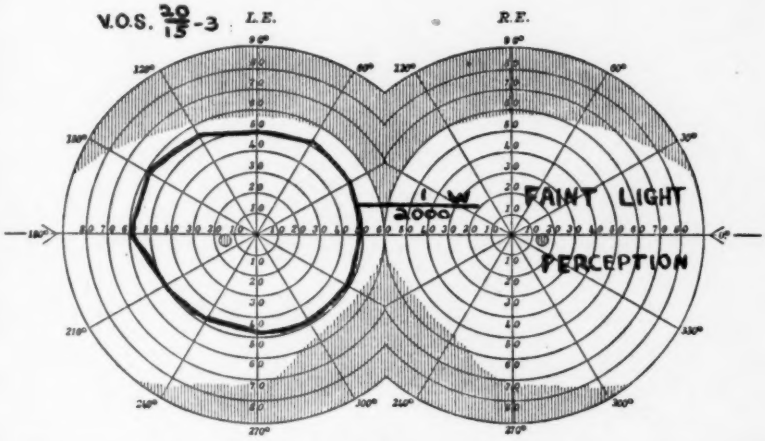

Fig. 12 (case 3).—Visual fields before operation (Oct. 22, 1941): normal vision in the left eye and the right eye practically blind.

Pathologically, this case must be regarded as one of the relatively rare instances of fibromatosis of the optic nerve, of which Hudson recorded 6 in his total series of 154 cases of tumor of the optic nerve.

CASE 3.—M. O'B., a single white girl aged 18, was seen at the Lahey Clinic on Oct. 10, 1941. She was referred by Dr. James C. McAdams, of Fall River, Mass. She complained of progressive loss of vision in the right eye during the fourteen months before examination. At the onset of her complaint the patient had first noticed blurring of vision in the right eye. The impairment in vision had been progressive, and when she was seen here practically no sight remained in the involved eye. She had never had any difficulty with the left eye. She recalled that in 1938 she had a series of severe headaches, lasting about a year. These attacks were chiefly fronto-occipital and required hospitalization. No diagnosis was made, however. In 1941 the patient had a period of unconsciousness, the duration of

which was not stated. Again, she was hospitalized for two weeks, but no diagnosis was made.

Examination revealed that the right pupil was slightly larger than the left and that the right pupil did not react well to light as compared with the left. The right fundus showed 4 D. of what was taken to be papilledema. The left fundus was normal. Extraocular movements were normal.

The exophthalmometric readings, with a base line of 95, were 19 mm. in the right eye and 17 mm. in the left eye. Visual acuity in the right eye was little more than faint light perception; that in the left was good, being 20/15—3. Since the patient was practically blind in the right eye, the visual field on this side was not obtainable. The visual field on the left side was normal, with a 1 mm. test object at 2 meters (fig. 12).

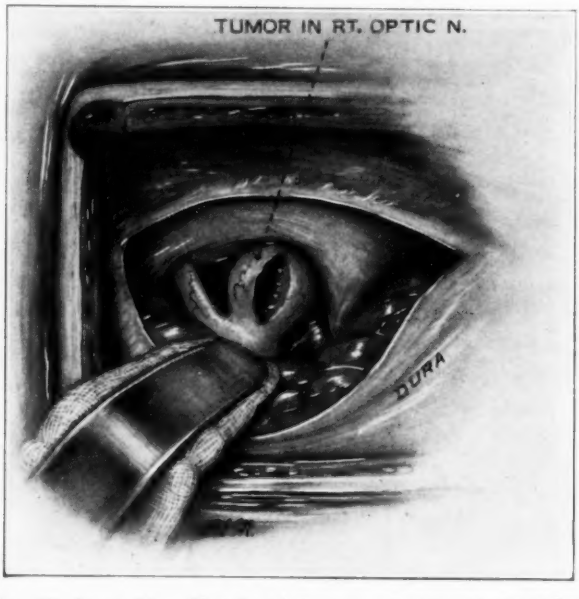

Fig. 13 (case 3).—Sketch of tumor, as seen at operation.

An encephalogram, made on October 23, revealed an essentially normal condition. There were no pathologic changes in the sella turcica. Complete studies of the urine and blood, including the Hinton test, revealed nothing abnormal. Lumbar puncture showed an initial pressure of 140 mm. of water; the fluid was clear and colorless, and the dynamics were normal. The total protein content of the spinal fluid was 40 mg. per hundred cubic centimeters. The Hinton and Wassermann reactions of the spinal fluid were negative. In view of the history and laboratory and clinical observations, a tentative diagnosis of tumor of the optic nerve was made.

Operation.—On October 27, a right frontal craniotomy was performed. The right frontal lobe was retracted, and the region of the right optic nerve was brought into view. Notes made by one of us (G.H.) concerning the operative observations were as follows: "It was at once apparent that the right optic nerve was greatly enlarged and somewhat red as compared with the left nerve, which was of normal size and contour. No tumor appeared between the nerves; there-

fore, it was fairly obvious that the enlargement and swelling of the right optic nerve represented a tumor of the nerve itself [fig. 13]. The nerve sheath was incised, and the tumor tissue was removed with a pituitary spoon. The growth extended backward into, or almost into, the chiasm, so that it was not feasible to resect the nerve at its junction with the chiasm, as I had at first hoped to do. The operation, therefore, was left as an intracapsular evacuation of tumor from the substance of the right optic nerve."

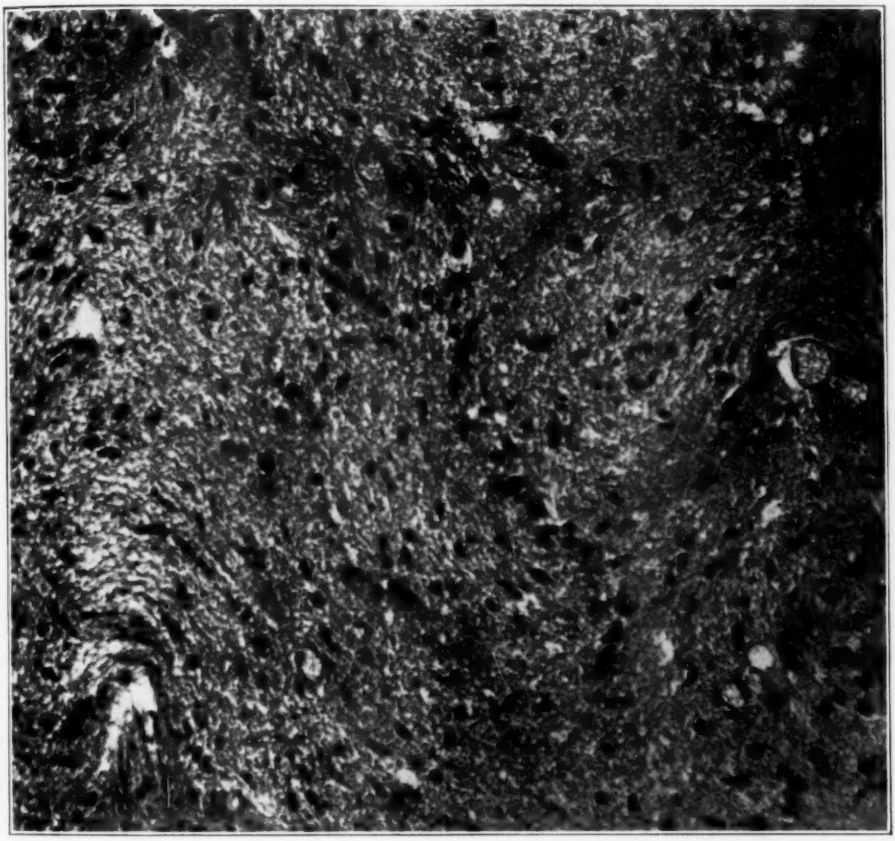

Fig. 14 (case 3).—Photomicrograph of tumor, composed chiefly of fibrillary astrocytes; × 350.

Pathologic Report.—The tissue was composed mostly of astrocytes, separated by a fibrillary ground substance. An occasional large vesicular astrocyte was noted. With the phosphotungstic acid hematoxylin stain, the presence of these glial fibrils was confirmed. This increase in glial fibrils and astrocytes and lack of much evidence of degeneration were consistent with the diagnosis of a fibrillary astrocytoma (fig. 14).

The patient did extremely well after operation and was discharged on the thirteenth postoperative day. Five months later (April 9, 1942) she reported for examination. She still showed slight exophthalmos of the right eye (fig. 15), and vision was unchanged.

The patient returned April 27, 1946 (four and one-half years after operation) for another examination. She was getting along extremely well and had no complaints other than the blindness of the right eye. She had been married during the past year. The right fundus was pale, and about 1 to 2 D. of protrusion was still present. The slight exophthalmos on the right measured the same as before operation. Visual acuity and visual field in the left eye were nearly normal (fig. 16).

Fig. 15 (case 3).—Photograph of patient five months after operation, showing slight exophthalmos of the right eye, as before operation.

Comment.—As with our other 2 patients, this woman's chief, and practically only, complaint was the progressive visual failure in one eye, ending in blindness. In view of the lack of other evidence of the more usual conditions in the suprasellar region, and because of blindness in one eye with a normal field and normal acuity in the other, a preoperative diagnosis of a tumor of the intracranial portion of the right optic nerve could be made with a fair degree of certainty.

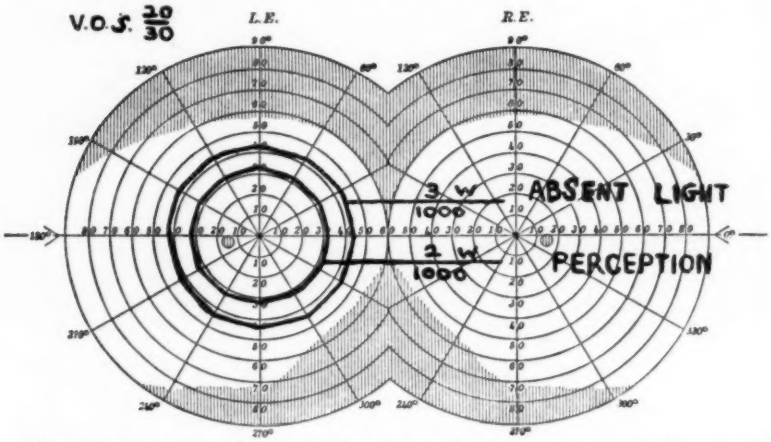

Fig. 16 (case 3).—Visual fields and acuity four and one-half years after operation (April 27, 1946).

One other clinical feature should be noted, namely, the appearance of the right optic disk. The enlargement was thought at first to represent unilateral papilledema; but later, when all the other features, including normal spinal fluid pressure and encephalographic abnormalities were taken into consideration, it was apparent that the protrusion of the

right disk was due doubtless to an extension into it of the presumed glioma, since before operation such a growth was thought to be most likely. It is likewise interesting that this protrusion before operation was measured as 4 D., whereas at a check-up examination by the same examiner (G.H.) five months after operation, April 9, 1942, this protrusion had receded to 1 to 2 D.

GENERAL COMMENT

Obviously, one is not justified in drawing far-reaching conclusions from so few cases as are here reported. However, these 3 cases serve well to emphasize that the prognosis of intracranial tumor of the optic nerve is not uniformly hopeless. Nor would it be fair to judge that the prognosis is as good as the report in at least 2 of these cases seems to indicate. The significant fact is that all patients with a verified lesion of this type are not faced with fairly rapid and completely bilateral loss of vision and may survive for an indefinite period, with perhaps only their unilateral visual defect to handicap them.

Visual failure in cases of chiasmal tumors, however, may be steadily progressive within a few months. The patient is often blind in one eye by the time a specialist is consulted, and vision in the other eye may be considerably impaired. It is interesting to note, however, that in the 3 cases reported here visual acuity in the unaffected eye remained good.

The fundi of all 7 cases reported by Martin and Cushing revealed atrophy of the optic nerve. In 5 of these cases it was definitely primary in type. In only 3 of 118 cases of intraneural tumor of the optic nerve reported by Hudson were the fundi normal. Instead of optic nerve atrophy, a certain number of the patients will present a fundus which resembles that of optic neuritis or early papilledema. The latter picture is sometimes difficult to distinguish from actual spread of the tumor into the globe in the region of the nerve head. However, such a distal spread of the tumor is said to be rare. Our case 3 is apparently an example of this feature. The normal spinal fluid pressure and the normal fundus in the opposite eye in this case support such an impression.

Association of neurofibromatosis with a tumor of the optic nerve has been noted on several occasions and was dwelt on in great detail by Davis.[5] An intraneural or extraneural growth of the optic nerve in such cases may well be a part of the underlying condition causing disseminated neurofibromatosis. In cases of obvious Recklinghausen disease one should be alert to the possibility that neurofibromas or other tumors may arise wherever there are nerve tissues. The optic nerve is not immune.

It should be remembered that a patient with a tumor of the optic nerve, apparently confined to the orbit or the portion of the nerve just

posterior to it, may harbor a neoplasm that usually spreads intracranially. The prognosis of such a growth is not so hopeless as it was formerly believed. Embryologically, it is in fact a tumor of the brain. The extraneural tumors of the optic nerve, like the meningiomas, can be cured by their removal. The patient with an intraneural tumor of the optic nerve, like a glioma of the brain, can be helped perhaps for a few years, and sometimes much longer. The ophthalmologist and the neurosurgeon, by coordinating their efforts in the treatment of these patients, can do much to prolong life and preserve remaining vision.

SUMMARY

Tumors of the optic nerve were classified by Verhoeff as intraneural (gliomas) and extraneural (meningiomas or endotheliomas). In addition to these two types, Hudson described a condition which he designated as fibromatosis. Case 2 reported here would seem to fall into this category.

Any type of tumor of the optic nerve may spread intracranially or intraorbitally or in both directions.

Failure of vision in one eye combined with some degree of exophthalmos, together with a normal visual field and visual acuity in the other eye in a patient showing no other evidence of an intracranial lesion, should speak strongly for the diagnosis of a tumor of the optic nerve within the skull.

Three cases of intracranial tumor of the optic nerve with survival from four and one-half to twelve years are reported.

The prognosis for patients having these tumors is not as consistently poor as is the general belief.

Dr. M. T. Trumbull and Dr. W. A. Meissner, of the department of pathology of the New England Deaconess Hospital, described and interpreted the microscopic sections of these tumors.

605 Commonwealth Avenue.

News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

The Albert D. Frost Memorial Library.—The department of ophthalmology of the Ohio State University College of Medicine, Columbus, Ohio, announces the opening of the Albert D. Frost Memorial Library, following Mrs. Frost's gift of her husband's ophthalmologic library. Plans for a study room in connection with the library in the new medical center are being made. To maintain the library, an endowment fund is needed, and an appeal is made to Dr. Frost's friends and others who might be interested in this worthy undertaking. Contributions of $5 to $25 are solicited. Checks are to be made out to the Frost Memorial library and sent to Arthur M. Cullen, M.D., University Hospital, the Ohio State University.

Albrecht von Graefes Archiv für Ophthalmologie.—This journal has resumed publication under the editorship of E. Engelking, W. Löhlein, O. Marchesani and K. Wessely. It is to be published by Springer Verlag, Heidelberg and Berlin, and J. F. Bergmann, Munich.

SOCIETY NEWS

Ophthalmological Society of the United Kingdom.—The annual congress of the Ophthalmological Society of the United Kingdom was held on April 8, 9 and 10, 1948, with A. J. Ballantyne, M.D., LL.D., president, presiding. The program consisted in a discussion of "Subjective Disorders of Vision" (excluding those due to local ocular diseases), which was opened by Prof. H. Cohen, Dr. Denis Williams and Mr. J. H. Doggart. The Bowman Lecture for 1948 was delivered by Prof. Marc Amsler, of Zurich, Switzerland, on "New Clinical Aspects of the Vegetative Eye."

The following papers were presented: "Ocular Palsies Due to Infection of the Nasal Sinuses," Dr. Helen Dimsdale and Mr. D. G. Phillips; "Preliminary Survey of Forty-Five Consecutive Cases of Congestive Glaucoma," Mr. J. P. F. Lloyd; "Conjunctival Nevus and the Neurogenic Theory of Melanoma," Mr. Eugene Wolff; "Venous Pressure in Glaucomatous Eyes." Dr. T. L. Thomassen; "Observations on Clinical Perimetry," Dr. G. I. Scott; "Two Cases of Special Interest: (*a*) A Subconjunctival Rupture of the Globe with Extensive Migration of Uveal Pigment, and (*b*) Aneurysmal Varix of the Retina," Mr. G. T. W. Cashell; "Papilledema Associated with Toxic Hydrocephalus," Mr. A. G. Cross; "Latent Nystagmus," Mr. T. Keith Lyle; "Classification of the Unassociated Dystrophies of the Fundus," Prof. Arnold Sorsby; "Prognosis in Detachment of the Retina," Mr. C. Dee Shapland; "Mode of Development of the Vascular System of the Retina, with Observations on Its Significance for Certain Retinal Diseases," Dr. I. C. Michaelson; "Atropine in the Treatment of Glaucomatous Iridocyclitis," Prof. W. H. Melanowski. A film, "Autoversion of the Upper Lid (left), Voluntary, Unaided," was shown by Dr. W. C. Souter, and two pictorial demonstrations were made: "(*a*) Spasm of the Central Artery of Retina; (*b*) Entroptic View of Retinal Vascularization; (*c*) Hypophysial Tumor Causing Homonymous Hemianopsia; (*d*) Hypophysial Tumor Causing Paralysis of the Third Nerve, and (*e*) Depigmentation of Iris in Chronic Glaucoma," Dr. H. M. Traquain, and "(*a*) Pressure Grafting in the Contracted Socket; (*b*) Epibulbar Dermoid Before and After Operation, and (*c*) Gummatous Ulceration of the Eyelids," Dr. J. Ellison.

Society Transactions

EDITED BY DR. W. L. BENEDICT

AMERICAN OPHTHALMOLOGICAL SOCIETY

John W. Burke, M.D., *President*

Walter S. Atkinson, M.D., *Secretary-Treasurer*

Eighty-Second Annual Meeting, San Francisco, June 26, 1946.

Cataract Complicating Glaucoma. DR. BERNARD SAMUELS, New York.

This paper was published in a previous issue of the ARCHIVES (**38**:353 [Sept.] 1947).

DISCUSSION

DR. J. L. MCCOOL, San Francisco: One of the most important decisions the ophthalmologist must make is to know when to tell the patient of the presence of a cataract and how much to tell him. Eventually, in the vast majority of cases, simple chronic glaucoma will be complicated by opacities in the lens.

In the case of a young person with a clear lens, one should say nothing until opacities develop and then tell the patient frankly of the outlook. Before operating for glaucoma, it is best to tell the patient that he has a complicating disease which will eventually require further operation.

If the opacity in the lens has developed to a point where it is the major factor in the reduction of vision, I have combined a tension-reducing operation with extraction of the lens. A large conjunctival flap, such as is used in trephining, is laid down to the limbus, or moderate splitting of the cornea is carried out. A wide corneal incision is made with a Graefe knife, and a large scleral flap is made when the incision is completed. A number of small bites are then made in the scleral flap with a Berens forceps; a broad, deep iridectomy is performed, and the cataract is removed in its capsule.

Development of the Ectodermal Framework of the Optic Nerve, with Especial Reference to the Glial Lamina Cribrosa. DR. HENRY C. HADEN, Houston, Texas.

The author showed a series of fifteen slides made from photographs of sections of human embryos and fetuses illustrating the development of the ectodermal framework of the optic nerve and the formation of the glial lamina cribrosa. At about the 15 mm. stage the undifferentiated epithelial cells in the wall of the optic stalk are stimulated by the entrance of the optic nerve fibers into the stalk to change into glial cells, which constitute the framework of the optic nerve. At the 67 mm. stage mesoderm begins to grow into the nerve from the anlage of the pial sheath and replaces most of the glial cells, forming the definitive fibrous connec-

tive tissue septums of the optic nerve. The lamina cribrosa is formed by the ingrowth of fibrous connective tissue from the sclera, and thus forms the lamina scleralis. The portion of the nerve anterior to the lamina scleralis remains ectodermal, and this portion is called the glial lamina cribrosa.

Mercury in the Lens (Hydrargyrosis Lentis). DR. WALTER S. ATKINSON, Watertown, N. Y., and DR. LUDWIG VON SALLMANN, New York.

A rose-brown homogeneous reflex from the lens which occurs in persons who have worked with mercury a long time or have chronic mercurialism was discussed and studied. Sections of the lens processed by Christeller's stannous chloride fixative showed black and dark brown deposits.

The mercurial nature of these deposits was confirmed by additional microchemical tests, as well as by spectrographic determinations. A case was reported.

Evaluation of Methods and Results of Cataract Operations as Performed in Private and Clinic Practice at Stanford University Hospitals. DR. HANS BARKAN, San Francisco.

The author reviewed his method of cataract extraction in 584 extracapsular and 187 intracapsular operations on so-called senile cataracts in the previous five years. The visual results in both types were recorded, as well as the incidence of postoperative complications. The author expressed the belief that a cataract operation involving a relatively short period, with the absence of sutures unless really indicated, a minimum of traumatic manipulation and careful consideration in each case as to whether the visual result desired will be obtained as well with the intracapsular method has in the long run obtained a satisfactory percentage of useful and satisfactory vision.

The author uses the Viennese school of cataract extraction except that the speculum is employed to hold the lids apart, akinesis is included and sutures are placed in the superior rectus muscle in all cases and retrobulbar injection is used in practically all intracapsular operations and in few of the extracapsular operations. Two corneoscleral sutures are used in all cases of intracapsular extraction but in few cases of extracapsular operation. The operator sits at the right side of the patient and operates with either hand. The Graefe knife is used. The Hess shovel is used to remove debris. A total iridectomy is done in 20 per cent of extracapsular extractions

Keratitis Due to Cephalosporium. DR. ARTHUR J. BEDELL, Albany, N. Y.

The second case on record of infection of the cornea with a species of Cephalosporium is reported. The corneal ulcer was the result of an abrasion caused by a cow's tail. The first laboratory reports implicated Staphylococcus albus and a few gram-positive cocci. However, sulfathiazole and penicillin were ineffective; and, since the author suspected a mold, treatment with potassium iodide was instituted, with satisfactory regression and subsequent culture of the cephalosporium. Photographs were included.

Healing of Corneal Wounds: II. Variations in Adhesive Power of Fibrin in in Vitro Studies. Dr. Albert L. Brown and Dr. Frank A. Nantz, Cincinnati.

The remarkable tenacity with which corneal wounds are sealed in the rabbit suggested the employment of fibrin in the repair of corneal wounds in man, for such natural formation in the aqueous of man is practically nonexistent. To this end, the role of fibrin in the cycle of corneal healing in the rabbit and dog was studied in vivo, as reported in the first paper on this subject. The present paper deals with in vitro experiments. In the living rabbit, fibrin seals a corneal wound mechanically until fibrosis can become established. It is difficult to determine exactly when fibrinolysis begins, but in vitro maintenance of a constant level with a gradual loss in adhesive power over eight days demonstrates the mechanical course outside the body. It was found that plasma and platelets in the human wound lend adhesive power to the edges of the wound.

DISCUSSION

Dr. Theodore L. Terry, Boston: The work on this subject with which I am familiar, relating largely to problems of war wounds, has not adapted itself to ocular injuries in practical ways. The fibrin film produced by Cohn and associates is not easily stitched into place, and the sutures pull out easily. Cohn's skin grafting unit, however, is of considerable interest. Solutions of fibrinogen and thrombin are readily made by adding a saline solution to the dry preparations. The one is painted on the raw under surface of the skin to be grafted, and the other is painted on the bed of the graft. Fibrin is formed when the graft is placed in its bed, thus obviating the necessity of stitches. It has a use in plastic operations on the lids.

Dr. Albert L. Brown, Cincinnati: We are not sure of the exact use as yet.

Treatment of Staphylococcic Corneal Ulcerations with Antitoxin. Dr. James H. Allen, Iowa City.

Corneal lesions occurring in the course of staphylococcic blepharoconjunctivitis are of two types: (1) superficial punctate epithelial keratitis and (2) marginal corneal ulceration with underlying stromal infiltration, iritis and occasionally progression to a ring ulcer. In 25 cases of the second type staphylococcus antitoxin was given and the only additional treatment was instillation of a 0.2 per cent aqueous solution of scopolamine hydrobromide for photophobia. A rapid response was obtained, furnishing clinical proof of the theory that toxin is an important factor in the production of this lesion. The administration of staphylococcus toxoid caused recurrence in 3 patients.

Since antitoxin therapy is of transitory effect, it is of practical value only in cases of severe staphylococcic infections in preventing permanent and irreparable damage to the cornea and should be followed by active immunization, chemotherapy or antibiotic therapy. It should also be useful in severe infections caused by penicillin-resistant strains. Serum sensitivity tests must be made.

Illustrations were given.

DISCUSSION

Dr. William H. Crisp, Denver: An injection of typhoid and paratyphoid U.S.P. containing 20,000,000 or 25,000,000 organisms was given a girl aged 18 during an acute attack of conjunctivitis, with great swelling of the lids, severe swelling of the bulbar conjunctiva and a great deal of discharge; the condition had been resistant to penicillin given intramuscularly four times a day for two days. From the beginning, the reaction to the typhoid and paratyphoid vaccine was remarkable, and the eye was practically restored to normal in twenty-four hours. Some older methods may at times be just as good as, or even better than, the modern methods.

Dr. Alexander E. MacDonald, Toronto, Canada: There is a vogue in ophthalmology, as well as in other medical specialties, to follow antibiotic treatment, to the exclusion of the older methods of therapy. I think I was the first to report the value of toxoid, and I wish to congratulate Dr. Allen on calling attention to the great value of this method of therapy.

Dr. James H. Allen, Iowa City: Typhoid therapy is of considerable value in the treatment of conjunctival and corneal lesions. However, in a case in which the globe was lost typhoid therapy was used but the lesion was not controlled. Treatment with antitoxin will control the acute manifestations rapidly, but the patient has to have a long series of injections.

Value of Corneal Peeling or Corneal Resection in Ophthalmology.
Dr. George L. Kilgore, San Diego, Calif.

A summary of the historical methods of medical and surgical removal of corneal scars and opacities was given. The author uses the technic for corneal resection suggested by Weiner and Alvis except in cases in which the corneal tissue is to be resected for one half or more of its thickness. In these cases, he found that there is less danger of damage to the posterior corneal lamellae if isotonic solution of sodium chloride is first injected along the line of initial incision. Preoperative and postoperative management was described in detail. Scars and opacities can be removed with relative safety, especially if they lie in the superficial layers of the stroma. Visual improvement compares favorably with the results of keratoplasty when scars are superficial and a donor is not necessary. Aphakia is not a contraindiction. Resection is the operation of choice in cases of certain dystrophies, recurrent extensive pterygium and symblepharon and a cornea with a small transparent area when keratoplasty is not advisable. Disfigurement of the eye by a reflex from a white corneal scar can be lessened by the replacement of superficial layers with transparent tissue. Irregular scars subjected to repeated ulceration can be removed, with relief of symptoms.

Three cases were reported.

DISCUSSION

Dr. Conrad Berens, New York: I wish to confirm the statements concerning the practical value of this operation. For about twelve years I have been performing a similar keratectomy. At first I tried simple excision with a cataract knife, with good results, but later found that in introducing the knife the heavy side made a deeper incision on one side than on the other. A knife was made for me by V. Mueller & Co., hol-

low ground on one side and curved on the back, which produced smoother scars.

I have been unable to determine whether there was less corneal scarring with the use of air injection, either in the rabbit or in the human eye.

Concerning results, I should like to mention a case of corneal scarring from a chemical burn in which I performed a superficial keratectomy after the method I mentioned and obtained 20/100 vision. This man had a seriously damaged eye, and I had to perform a deep excision, and even perforated the cornea. Later, I thought perhaps better vision might be obtained with a corneal transplant. Secondary glaucoma developed, however, and it was finally necessary to remove a cataract, which was probably traumatic in origin. Final vision was only 5/200.

There are many complications from corneal transplantation which make one hesitate in employing it. In a case of corneal dystrophy removal of the superficial layers of the cornea resulted in secondary scars, with only slight, or no, visual improvement. In a selected case I prefer to remove the superficial layers of the cornea by some method rather than perform a corneal transplantation. I have had troublesome complications from superficial keratectomy in only 2 cases—in 1, the development of a small central, superficial, painful capillary angioma after keratectomy for a burn of the cornea with steam, and in the other, a sensitive, superficial vascularized lesion in a man with recurrent keratitis of undetermined origin.

DR. GEORGE L. KILGORE, San Diego, Calif.: The results of this particular operation, are, of course, dependent on a clear cornea, and, as I brought out in the paper, I believe any diffuse scarring of the cornea with involvement of the deeper layers is a contraindication to an operation of this type. I believe that in those circumstances the prognosis for good vision is poor.

Pigmentation of the Palpebral Conjunctiva Resulting from Mascara. DR. ALGERNON B. REESE, New York.

Six cases of pigmentation of the palpebral conjunctiva in women from 31 to 55 years of age were described which was thought to be due to the use of mascara or similar pigment-bearing cosmetics. It was concluded that some personal factor determines the occurrence of the lesion. The condition appeared as a granular, stippled pigmentation under the palpebral conjunctiva of both upper lids occurring as a narrow line at the upper border of the tarsus. The color varied from black to dirty light brown. Folliculosis was always associated. There were only mild symptoms.

Five excellent illustrations were shown.

Diagnosis of Early Glaucoma. DR. HENDRIE W. GRANT, St. Paul.

In the presence of symptoms of unrelieved asthenopia, subnormal or unequal accommodation, a variation of more than a few millimeters in the tension of the two eyes, sclerosis of the nucleus of the lens or a history of glaucoma in the family, one should institute a searching examination for evidence of early glaucoma. Contraction of the peripheral fields and cupping of the optic nerve are late symptoms. Although the ocular

tension may be found to be normal on routine determination, enlargement of the blindspot is present if the tension has been recently elevated.

The author presented data in 27 cases of increased intraocular pressure without evidence of cupping of the optic nerve or changes in the peripheral fields; 1 case of slight cupping with increased tension found on only one occasion, in the early morning, and characteristic changes of glaucoma; 2 cases of acute congestive glaucoma with the fellow eye showing a shallow anterior chamber, normal tension and enlargement of the blindspot, and 3 cases of enlargement of the blindspot and symptoms suggestive of glaucoma but without evidence of increased intraocular tension.

DISCUSSION

DR. WALTER W. WRIGHT, Toronto, Canada: Dr. Grant has covered the scientific aspect of the early diagnosis of glaucoma. But we must not forget that we are physicians as well as scientists. Three patients whom I saw recently had all, I felt, been made much worse by having had a diagnosis of early glaucoma and had been greatly worried about it.

DR. RALPH I. LLOYD, Brooklyn: Von Graefe classified glaucoma under three types: acute glaucoma, chronic glaucoma and excavation of the disk with amaurosis. He stated further that hardness of the eyeball, excavation of the disk and displacement of the vascular stalks often develop before demonstrable changes in the field. Hoffman, of the Donders clinic, stated that "contraction of the fields occurs in all forms of glaucoma, but in glaucoma simplex it is not the first symptom."

Much the same ploblem exists today. There is little likelihood that cupping or elevation of tension will be overlooked. Field work is subjective and is held by many in low esteem, but the importance of its use should be emphasized.

Some patients who have had refraction at regular intervals will show cupping of the disk but not changes in their visual fields or increase in tension. After several years typical field defects may develop, but the tension will remain well within normal limits. Late in the course of the disease the tension may rise, but the condition in some patients goes on to blindness without increase in tension. In the cases with delayed or no rise in tension, there is not much hope of improvement. In the cases in which there is no rise of tension, the condition is probably not glaucoma at all but is due to pressure of sclerosed portions of the circle of Willis or to isolated patches of sclerosis in the nerve trunk, as shown by Fuchs. Some authors have claimed that in cases of the latter types the rise in tension occurs in the early morning, or at other times of the day, and may escape detection. Some assert that in these cases the glaucoma may be tested for by producing a sudden increase in blood pressure by having the patient drink water or plunge an arm into hot water and then into cold water.

DR. PETER C. KRONFELD, Chicago: Some of the enlargements of the blindspot described by Dr. Grant are of the order of the Seidel sign, and therefore of great diagnostic significance. Enlargements due to the addition of crescent-shaped areas laterally are more difficult to interpret, especially if the development of the tissue bordering on the nerve head is not typical.

I agree with Dr. Grant that a definitely glaucomatous defect in the visual field is of greater diagnostic significance than the actual observa-

tion of an elevated ocular tension on one occasion, because the glaucomatous field defect is indicative of many periods of increased ocular tension. That it takes many early morning periods of slightly increased tension to produce the earliest demonstrable changes in the field may be learned from observations on low tension glaucomas, which are refractory to miotics.

The actual equipment for tonometry is at its lowest point. However, new tonometers are soon to be available which will conform to the specifications for Schiötz tonometers, as stipulated by the Committee on Standardization of Tonometers of the American Academy of Ophthalmology and Otolaryngology.

The consistency of the reading obtained with the Gradle tonometer was much lower than that of readings obtained with most Schiötz tonometers, probably because the Gradle instrument has a foot plate curvature of 9 mm., whereas that of the Schiötz tonometer is 15 mm. The latter, moreover, produces a similar deformation of all human corneas (except pathologically flat ones), whereas the Gradle instrument deforms only the more strongly curved ones.

When accurate and durable tonometers become available, tonometry will come into its own again and will probably become the most valuable single means in the diagnosis of the glaucomas.

DR. HENDRIE W. GRANT, St. Paul: As Dr. Wright said, it is possible that a patient might have a neurosis following the diagnosis of early glaucoma provided he were not properly managed. I have not seen any instances in which the neurosis persisted if the patient was properly advised as to his condition.

In addition to the cases cited, there were 2 instances of shallow anterior chamber with enlargement of the blindspot but no elevation of tension, as well as 3 cases with early symptoms of glaucoma, an enlarged blindspot but no increase of tension. The latter type presents a really difficult problem.

Use of a mydriatic not only may fail to produce an increase in pressure but may actually cause a reduction of pressure. This is true in some cases of deep angle glaucoma.

Chemical Natures of the Aqueous Humor in the Glaucomas.
DR. PETER C. KRONFELD, Chicago.

In the normal eye, as well as in the eye affected with deep chamber glaucoma, the ascorbic acid level of the aqueous is dependent on that of the blood. Determinations of the ascorbic acid content of the aqueous have failed to throw light on the mechanism of deep chamber glaucoma.

No relation was found in normal controls between the ascorbic acid level and the protein content of the aqueous. There appears to be a relation between the intraocular pressure and the protein content of the aqueous in the sense that at the higher pressures the blood-aqueous barrier becomes more permeable.

In 2 cases which were investigated the glaucoma was unresponsive to miotics, and the values for ascorbic acid were low, leading the author to postulate that the combination of low vitamin C intake with unrelieved glaucoma of long standing may be conductive to low values for ascorbic acid in the aqueous.

DISCUSSION

DR. THEODORE L. TERRY, Boston: Recently, my associates and I have tried to establish in various laboratory animals by quantitative measurements of ascorbic acid the time when the aqueous humor takes on the adult character, but the work was not completed early enough for presentation here. The change in the ascorbic acid level in relation to glaucoma appeared interesting. Could the reduction be an indication of the activation of a process which led to cataract formation?

DR. PETER C. KRONFELD, Chicago: I believe that ascorbic acid is the most suitable substance to define as the specific product in the adult aqueous, but proteins and ascorbic acid should be determined in the same specimen. In neither of the aforementioned cases with low ascorbic acid levels were there signs of cataract. Even if there were, that would not have led one to expect a low ascorbic acid level of the aqueous, since only mature and hypermature cataracts are associated with ascorbic acid values as low as those shown in these 2 cases of deep chamber glaucoma.

Ophthalmology During the War and in the Future. SIR WILLIAM STEWART DUKE-ELDER, London, England.

The distinguished ophthalmologist briefly reviewed the developments in ophthalmology during the war years and offered predictions as to the direction of future investigations. In ophthalmic surgery, technics of dealing with intraocular foreign bodies were revolutionized, and the ingenious Berman locator was devised. Concepts of the minute central localization of the visual functions were put on a secure observational basis. Novel and fruitful suggestions in the fitting of artificial eyes were made. In ophthalmic medicine, the greatest advance was made in chemotherapy. Knowledge of the optics of gunsights, range finders, periscopes, graticules and viewing and scanning devices; uses of goggles; problems of dazzle, scatter and haze, and, above all, of night vision and dark adaptation have increased beyond all bounds.

Real advances were begun in two lines of investigation: the study of the performance of the eye at high altitudes and that of the scotopic, or rod, fields. A microelectrode was devised which picks up and amplifies changes in potential of a single fiber in the optic nerve when a cone or rod is stimulated by light. With elaboration of these two technics, great advances should be made in knowledge of the mechanism of photoreception.

New studies on the formation and circulation of the aqueous are being made. With the electron microscope and radioactive tracer elements, new studies on the physiology of various parts of the eye are in progress.

The author stated the opinion that ophthalmology is on the threshold of many important and far-reaching discoveries.

Visual Disturbances Due to Digitalis. DR. D. F. GILLETTE, Syracuse, N. Y.

A historical summary of the visual disturbances ascribed to digitalis was given, and 3 of the author's cases were presented. The visual disturbances recorded in the literature are flickering of light, occurring

early, followed by chromatopsia, which may be ushered in by an intense white appearance of light objects. These white objects often have a colored border, usually blue or lavender, which may later spread out and cover the entire object. In other cases, the objects appear to take on a yellow, orange or green color. Other disturbances found by various authors are indistinct, dim, disturbed or confused vision; headaches; amblyopia; nystagmus; mydriasis; diplopia, and conjunctivitis.

In the author's cases visual disturbances developed in each of two or more courses of administration of digitalis. The symptoms, which increased in severity for from twenty-four to seventy-two hours after withdrawal of digitalis, took from ten to fourteen days to disappear. In the first case there were flickerings of light, xanthopsia and dim vision, central retinopathy and a central scotoma; in the second case, blurred vision, pallor of the disks and a central scotoma; in the third case, xanthopsia, difficulty in reading and white, wavy lines.

DISCUSSION

Dr. S. Judd Beach, Portland, Maine: I have had a number of patients who complained of blue vision from digitalis, but none were taking the drug when they reached me, so that I can add little to the information already received. I should like to ask whether there is any other reason that most of these patients are at such an advanced age, other than that vascular lesions are more likely to develop with old age and require digitalis; and whether there is any information on why so few patients in proportion to the vast number who receive digitalis complain of these peculiar symptoms.

Dr. Albert L. Brown, Cincinnati: Apropos of Dr. Beach's comment that so many patients are digitalized but comparatively few show any visual disturbances, I should like to suggest a warning against digitalization of patients with advanced glaucoma. In the last five years I have seen patients with advanced chronic glaucoma who have had early and severe reduction in vision from the use of digitalis. One of my patients, aged 65, in poor general health, who had had a successful bilateral trephination for glaucoma, was subsequently digitalized and in one week had rapid reduction in vision, from 20/30 to 20/60, in one eye. He stated that he had noted peculiar colors but had thought it was part of his ocular condition. After cessation of digitalization, vision returned to 20/40.

A woman aged 66 required heavy digitalization and immediately complained of chromatopsia. Administration of digitalis was stopped immediately, and vision returned at once. A second, milder, attempt at digitalization had the same results; so quinidine was substituted, with no further visual disturbances.

Dr. D. F. Gillette, Syracuse, N. Y.: It is my belief that visual disturbances of digitalis origin are commoner than has been realized. They are commoner among patients of the older group, because these persons require the drug oftener. Then, too, in such patients sclerotic retinopathy is often already present. It will be interesting to check the tension in cases of visual reduction from digitalis, as suggested by Dr. Brown.

Ocular Changes in Acute Disseminated Lupus Erythematosus.
Dr. Frederick C. Cordes and Dr. Samuel D. Aiken, San Francisco.

A case of acute disseminated lupus erythematosus in a woman aged 30 was presented. The patient was observed clinically for six months be-

fore the fatal termination of the disease. Examination of the fundus revealed cotton wool exudates with small, irregular hemorrhages, as well as flame-shaped hemorrhages. There was papilledema. The most striking feature was the vascular changes. The veins were dilated and irregular in caliber, with perivascular thickening and small, isolated thromboses in the venous branches. The arterioles showed a spotty, disseminated distribution of very irregular, localized narrowings. In some areas there was complete occlusion, associated with perivascular thickening. There was also arteriolosclerosis. The changes in the arterioles may have been only the manifestations of diffuse hypertensive sclerosis. Microscopic examination showed subintimal thickening and sclerosis of the arteriolar and arterial walls, with narrowing of the lumens, and scattered, widespread occlusive lesions of the vessels, but none of the changes in the intimal endothelium usually considered characteristic of the disease.

The authors stated that they did not regard any single lesion, or combination of lesions, as pathognomonic of lupus erythematosus but that so-called toxic retinitis is the most typical and frequent in cases of acute disseminated lupus erythematosus.

DISCUSSION

Dr. L. F. Philip Koch, New York: This has been a thorough review of the literature and is especially valuable because of the report on the ocular changes in this acute systemic disease. Additional detailed reports on the ophthalmoscopic findings should provide sufficient information to lessen the confusion now existing in the early clinical diagnosis of this disease. It is my opinion that constant reobservation of the fundi will reveal the earliest signs, which I believe may be pathognomonic.

In the case reported, the intraocular lesions were not observed until fourteen months after onset of the disease, and from that time until death, there were numerous findings which were not sufficiently clearcut to rule out the coexistence of systemic hypertension. The presence of the latter was confirmed at autopsy. Thus, the question arises whether this case more properly should have been considered as representative of the Libman-Sacks or the Senear-Usher syndromes, since it is my opinion that at the beginning classic, or purely typical, acute disseminated lupus erythematosus is primarily a disease of the arteriolar and venous capillaries and that the morbid process slowly, but inexorably, extends more or less diffusely in a proximal direction.

The retinopathy, therefore, is essentially mechanical, and its variations depend on individual variations in tissue structure. These variations, when complicated by the ocular manifestations of systemic hypertension sequential to the visceral lesions in lupus erythematosus, will afford still greater difficulty in diagnosis unless the individual retinal lesions are studied minutely with reference to the entire retinal picture and are correlated carefully with the clinical picture as a whole.

Dr. Samuel D. Aiken, San Francisco: Since writing this paper, we have observed 3 additional patients ophthalmoscopically. Two are still under observation. One is a 17 year old girl, who has been followed fourteen weeks; the other is a woman aged 39, who has been observed four weeks. Both patients present strong clinical and laboratory evidence to support a diagnosis of acute disseminated lupus erythematosus. Except for mild dilatation of the retinal vessels, the fundi appeared normal.

The third patient, a woman aged 40, had one cotton wool patch and one small hemorrhage in the retina of one eye, and her condition was probably "toxic retinitis." The diagnosis was established by autopsy.

Lipemia Retinalis: Report of a Case. Dr. Ferdinand L. P. Koch and Dr. Paul S. Strong, New York.

This paper was published in a previous issue of the Archives (**38**:310 [Sept.] 1947).

DISCUSSION

Dr. George Stuart - Campion, San Francisco: I should like to show "kodachrome" slides of the fundus of 3 patients with lipemia retinalis.

The first picture is that of the left fundus of a white man, aged 29, who, when he entered the hospital in coma, had 1,660 mg. of cholesterol and 15 Gm. of total lipids, per hundred cubic centimeters of blood. He was known to be diabetic and to have strayed from his diet. The entire fundus was pale; the creamy, cordlike vessel seemed to cast a shadow, and the arterioles were indistinguishable from the veins except for size. The pallor and the opaque appearance of the vessels were due, of course, to the heavy concentration of emulsified fat carried in the blood stream.

For the second patient, a white man aged 27, the blood cholesterol measured 885 mg., and the total fat of the blood 5 Gm., per hundred cubic centimeters. He did not know that he had diabetes. The lipemia in this case was not as pronounced as in the other cases and cleared rapidly, as it always does, under a diabetic regimen.

The third patient, a white man aged 30, was unaware of his diabetic state. At the time the first picture was taken, the blood cholesterol was 2,000 mg., the total fat of the blood 10 Gm. and the blood sugar 242 mg., per hundred cubic centimeters. The second picture, taken sixteen days later, showed definite improvement, but the fundus was still pale and the vessels were cordlike.

Dr. Arthur J. Bedell, Albany, N. Y.: I present one picture of lipemia retinalis sent me several years ago by Dr. Grady Clay.

Dr. C. A. Clapp, Baltimore: While this is the sixty-sixth reported case, there are many more unreported. I should like to draw your attention to another type of lipemia retinalis, which is not diabetic but apparently is a familial type. Hold and others, in 1939, reported the case of an 11 year old girl from Johns Hopkins Hospital who had repeated gastric crises, extending over several months, each being followed by lipemia retinalis. It was interesting that one of her younger brothers had lipemia and that the mother had an increased amount of fat in the blood. This case was studied carefully, and it was found that the fat increased after administration of lecithin, choline, thyroxin, insulin, liver extract or anterior pituitary extract. The only treatment other than regulation of diet which lessened the lipemia was blood transfusion. The lipemia was fairly well controlled with a low fat diet, and the latest report in this case is that the patient has gone along for several years and that the lipemia has been controlled fairly well with a low fat diet.

A recent case, not reported, is that of a 9 year old boy, in which the lipemia retinalis was discovered on routine examination and it was found that several members of his family had increased fat in the blood and 1 had slight lipemia retinalis.

Dicumarol and Rutin in Treatment of Retinal Vascular Disorders. Dr. Angus L. MacLean and Dr. Charles E. Brambel, Baltimore.

Twenty-one cases of various vascular retinopathies, including occlusion of tributary veins, partial occulsion of the central vein, diabetic retinopathy, degenerative retinopathy, central serous retinopathy (angiospastic) and Eales's disease, occurring in persons from 34 to 72 years of age, were treated with dicumarol and/or rutin. The dicumarol was used for inhibition of the thrombotic process, and the rutin, for decreasing capillary fragility. In this series of cases there was a definite decrease in the prothrombin clotting time of dilute plasma as compared with that of normal controls. Increased capillary fragility was present only in cases of idiopathic hemorrhagic disease (Eales's disease).

The authors expressed the opinion that the absorption of the hemorrhages in these diseases was decidedly more rapid than could have been expected in cases without treatment.

Photographs of the fundus are included.

Pseudotumors of the Macula. Dr. Ralph I. Lloyd, Brooklyn.

The author reviewed and classified the various changes which simulate tumors of the macula, such as disciform degeneration of the macula, Coats's disease, senile and presenile macular degenerations, tuberculous lesions in young patients and idiopathic retinal detachment. The pathologic descriptions of these conditions, as well as several drawings, were included.

DISCUSSION

Dr. Arthur J. Bedell, Albany, N. Y.: Six photographs of the fundus were shown to illustrate the need of critical consideration of all details—vascular, retinal and choroidal—in the diagnosis of lesions in the macular region.

Senile macular degeneration can, by means of these pictures, be traced from its inception to its termination as an organized, elevated gray mass. Care must be taken to recognize this condition as vascular rather than neoplastic.

Dr. Algernon B. Reese, New York: A lesion belonging to this interesting group is one which arises from a massive intraretinal hemorrhage in the newborn, or as a result of trauma in early childhood. The organization of this hemorrhage leads to the formation of an elevated white mass, which may be confused with retinoblastoma. I have 12 cases of such a lesion. I reported several cases under the title "Massive Retinal Fibrosis in Children" (*Am. J. Ophth.* 19:576 [July] 1936).

In my opinion, the cause of this lesion is the same as that of a similar lesion which occurs in the brain; I refer here to the massive intracranial hemorrhage which occurs at birth and leads to the clinical picture of spastic paralysis. These conditions—massive intraretinal hemorrhage and massive intracranial hemorrhage—probably have the same causative factors. They stem from the same vascular system. An important etiologic factor is increased pressure in the jugular area, which is transmitted to the terminal vessels because there are no values in the jugular area to diminish the curse of this increased pressure. A contributing factor is perhaps the hypoprothrombinemia, which is known to be present during the first days of life.

DR. THEODORE L. TERRY, Boston: There must be some anatomic or physiologic reason that the lesion which Dr. Lloyd discusses is located in the macular region so frequently. It is possible, but improbable, that continuous, but subminimal, exposure to bright light is concerned. Reduction in vision often precedes visible pathologic change. Recently I saw a patient whose vision decreased from 20/15 to 20/30 in three weeks, but only on the third visit was edema of the macula visible.

The age of the patient helps to differentiate Coates's disease of the early decades of life and disciform degeneration of the third or later decades.

Angioma of the choroid gives a similar picture. This lesion may look like malignant melanoma clinically, but pathologic examination after enucleation may reveal nothing, as the choroid angiomas may have emptied and become invisible when the ocular vessels were severed. So far, my idea that angioma may be recognized by applying pressure to the globe to see whether the lesion disappears has not been tested thoroughly.

Careful measurements of the scotoma at intervals of a few weeks may show that the field defect is reduced in case of the so-called juvenile form of disciform degeneration.

Experimental Studies on Retrobulbar Neuritis. DR. P. J. LEINFELDER and DR. W. A. ROBBIE, Iowa City.

Because of many reports in the literature relating to the role of nutritional disturbances in retrobulbar neuritis and the possible association of cyanide poisoning, the authors subjected rats to a series of experiments in which diets were altered in various ways, and in various combinations of deficiencies of thiamine, the vitamin B complex and riboflavin, and in which the rats were fed a low protein diet and subjected to exposure to hydrogen cyanide gas.

In none of the experiments was significant degeneration in the optic nerves observed, even though the rats with deficiency in the vitamin B complex and those with thiamine deficiency were reduced to extreme degrees of malnutrition and were at the point of death at the time of the removal of tissue for examination. Conclusive evidence of injury to the ganglion cells was not obtained.

In an animal exposed to cyanide gas and made deficient in thiamine there was slight degeneration in the optic and sciatic nerves, but not enough, according to the authors, to warrant conclusions.

The "Duction Test"—An Evaluation of the Various Technics. DR. WALTER H. FINK, Minneapolis.

An analysis and evaluation of the commoner methods of testing ductions was made, and a plan was presented for a technic which is designed to secure more constant and dependable results. The author has tested 100 patients with 20/20 vision and a small refractive error, only patients with a small amount of heterophoria, normal accommodation and a normal near point of convergence being used. He recommended the use of the phorometer with rotary prism and the Snellen or rotating target, and he recorded the data for base-in and base-out prisms with both near and distant targets, measuring the blur-out, break and recovery points.

DISCUSSION

DR. WALTER B. LANCASTER, Boston: Of the tests of the power of convergence and divergence, I learn more from the so-called duction test than I do from measuring the heterophoria with the Maddox rod. These tests show the capacity of the patient to overcome whatever deviation is present, and this is more important than to know the amount of deviation.

I object to the term "duction test." The power of abduction and adduction of one eye is measured by covering the other eye and having the uncovered eye follow a finger to the right and to the left. If both eyes are examined together and rotated to the right and to the left, dextroversion and levoversion are measured. The first is properly the duction test, and the second is the version test. Vergence is the power of convergence and divergence.

The term "duction" is a term authorized by the optometrists, and it is incorrect. The orthoptists correctly use the term vergence. That is what it is—convergence, divergence and vertical divergence.

To demonstrate the importance of vergence tests, take a case of exophoria: Suppose there are 6 Δ of exophoria for distance and 12 or 14 Δ for near vision. When one tests the divergence for distance, the patient will be able to overcome prisms up to perhaps 12 or 14 Δ, base in. His break point will be 12 Δ and his recovery point 11 Δ, or his break point will be 14 Δ and his recovery point 12 Δ. The difference between the break and the recovery point is very small, indicating that the reflex is working efficiently—in fact, is stronger than is needed. Then one tests the patient's convergence with prisms base out. One finds that he gets diplopia at, say, 10 or 12 Δ of convergence. One then turns back to see where he will recover, and it is not uncommon to find that he does not recover well, and that his convergence power goes down to 6, 4, 2 or 0 Δ before he recovers. Not only is his amplitude of convergence small, but even more striking is his poor recovery as the converging prism is reduced. This shows that the converging reflex is working poorly and calls for active training of converging power. This procedure is a test of the reflex produced by images on the retinas of the two eyes which cause diplopia. Winking stimulates fusion in a manner similar to Dr. Fink's moving target and may be used in this test.

The room should be light, and there should be a Snellen chart or a red star on the wall. The reason for having the room lighted is this: If one has only a spot of light, the stimulus is on the macula, whereas if one has the end of the room lighted one gets a stimulus not only to the macula but to the periphery; and, as Dr. Burian showed, the power of the periphery of the retina to stimulate fusion is great.

The exact results in these measurements are not of importance, but the relation of the deviation and the break point and the recovery point are extremely important.

DR. AVERY DEHART PRANGEN, Rochester, Minn.: Dr. Fink's theme, as he expressed it to me, is that he utilizes the entire visual mechanism—the field of vision as well as central macular fixation. Instead of using a spot of light, he lights up the whole target, so that he is attempting to adapt the test of lifelike conditions, with the whole target instead of a small spot of light. I agree with Dr. Lancaster on the use of the term "vergence" instead of "duction." When one thinks in terms of vergence,

I believe one has a different, and better, concept of this important function.

Dr. Thomas D. Allen, Chicago: The test of the ability to converge and to diverge the eyes is one not of turning ability but of two cerebral functions: fusional ability and the ability to overcome relatively difficult obstacles. These two cerebral functions are skills that are not always easily used but are readily acquired, just as are writing and skipping rope; and they are of great value to one who does a good deal of comparatively close work.

My colleagues and I have now revamped our methods of muscle testing and do Maddox rod and cover tests and determine the near point of convergence routinely; if the results with these tests are not quite within normal limits, the cover test is used in the six cardinal positions, and the relative stereoscopic ability is studied. If there is found with these tests a convergence or a divergence deficiency, some simple orthoptic home treatment may be suggested to, or even urged on, the patient.

For suppression or for situations requiring more extensive training, we send the patient to the orthoptist, who can spend the necessary time to explain in detail and to institute a training schedule. Occasionally we use the major amblyoscope ourselves, and often the "jump-deduction" stereoscopic pictures.

The tests at the near point should be carried out with the gaze depressed about 20 degrees, as in reading.

Dr. Conrad Berens, New York: I find that many patients have difficulty with convergence. Dr. Fink used the rotary prism for making his studies and stated that he gets better results with it. One must decide what one means by better results. Twenty-five years ago, when we were working with the original Howe ergograph and used prisms for testing convergence, my associates and I realized that prisms introduced a factor which made our tests unreliable. We found it highly desirable to substitute a small dot or a line for prisms, and to take the near point of convergence repeatedly. Also, we found that taking the near point once or twice means very little. Dr. Fink emphasized that the test object to be used is of great importance. If a light is used, as is often done by my associates, because in using the Maddox rod they have the fixation light in their hands, and they report a near point of convergence of 70 mm. and a prism convergence for near vision of only 10 or 12 Δ, I suspect immediately what they have been doing. The studying of convergence with test type, as Dr. Fink brought out, brings us added knowledge of accommodative convergence.

I have never been pleased with rotary prisms. In the first place, when using a rotary prism in a phorometer, I find difficulty in seeing what the eyes are doing, which I think is most important. I prefer the prism rack or loose square prisms. The best method is to use one of the major stereoscopes to study fusional convergence against accommodative convergence. Also, in order to study convergence, a careful study of fatigue in convergence, and sometimes of divergence, should be made.

Dr. Walter H. Fink, Minneapolis: Undoubtedly, there are various methods of testing the vergence, but it seems logical that one method should be adopted; this would tend to eliminate much confusion, and one's results would be better interpreted by others.

Surgical Treatment of the Extraocular Muscles. Dr. Avery deHart Prangen, Rochester, Minn.

The author reviewed and summarized his experiences in extraocular muscle surgery during a long career. He mentioned many of the new developments and called attention to errors made in the past by surgeons who operated on the muscles of the eye. He called attention particularly to the necessity of careful and accurate preoperative diagnosis, and he gave many practical and worth while suggestions as to operative and postoperative care.

DISCUSSION

Dr. J. H. Dunnington, New York: I am in complete accord with the plea against undue conservatism, especially after the diagnosis is made and the patient is in the operating room. One should study the case carefully, make an accurate preoperative diagnosis, decide on what has to be done and do it. I agree that in the vast majority of cases a general anesthesia is preferable. I also urge the adoption of Dr. Prangen's suggestion of adequate exposure. In the preoperative diagnosis, I personally believe that prismatic measurement of the deviation is an essential part. Repeated tests are essential.

I do not agree with the author with respect to large recessions. I favor a recession, as a rule, of not more than 3.5 mm., even on the external rectus muscle, and I do not believe that a tentotomy of the external rectus can be done with impunity, since complete paralysis or partial limitation of motility may be produced.

I, too, use surgical gut sutures routinely. I agree with him as to simple postoperative care and do not use anything but light protective dressings for a few days.

Although I wrote on the subject in 1929 (*Tr. Am. Ophth. Soc.* **27**: 277, 1920), I never do a complete tenotomy of the inferior oblique muscle at its insertion without some form of scleral anchor, for I found that when this tenotomy was performed it produced a complete and permanent paralysis of the muscle. Recession or a myectomy at the origin of the muscle is the method of choice.

Dr. Conrad Berens, New York: I must confess that I, too, exercised undue conservatism formerly, for about the same reasons as those given by Dr. Prangen. Another reason is that I became imbued with the idea that one should do something more with orthoptics than attempt to obtain functional, and not merely cosmetic, results, and I was most anxious to see what could be done. I found out I could not do more than the patient could do with the fusion at his command; but, until I had sufficient experience, I expected the patient to obtain better results than he could possibly obtain. Now I operate much earlier than I did, and I believe that this factor is important in getting better results.

The mention of overconservatism raises the question of how many muscles one should operate on. In cases in which more than four muscles were operated on and surgical gut was used, particularly chromic surgical gut, I have had some severe reactions. With the use of "nylon" or silk sutures my reactions have been much less pronounced. I operate frequently on three or four muscles at a time; perhaps with more accurate diagnostic methods in the future one will operate on more. Recently I have operated on as many as five at one time. I think that one should

divide one's surgical procedures between the two eyes whenever possible, and so avoid underaction in some cases, a result which may be due to trying to do too much to one muscle.

Congenital anomalies have been most troublesome, especially with the inferior oblique muscle.

In performing the retroplacement operation, I have freed the inferior oblique muscle from its scleral insertion.

The matter of diagnosis is becoming increasingly important, and technicians are writing that they have given orthoptic training to patients without relief. In their opinion, this is because in many instances spasm of the inferior oblique was not diagnosed.

One thing which Dr. Prangen did not bring up, fas as I know, is the question of the fixing eye. I think the determination of fixation, not only in the primary position but also in the main diagnostic direction of gaze, is most valuable and should be a part of the preoperative record because of its great importance in determining what should be done surgically.

I know of no other test which has given me the accurate information, especially in the case of vertical deviations, which the screen and parallax test with prisms does. It is valuable and helpful, not only for diagnosis but also in the evaluation of postoperative results.

The clever idea of tying surgical gut sutures outside the conjunctiva, which Dr. Prangen suggests, I have not tried, but I have been using "nylon" sutures and have found them satisfactory. I have had a new suture developed by Davis & Geck, Inc., especially suitable for the inferior oblique muscle, or double-armed blue "nylon" (00000). The needle they have made is a little stronger and more curved, a feature which is important in operations on the inferior oblique.

With regard to resections of the lateral rectus muscles, I agree with Dr. Prangen as to the maximum amount, that is, 10 to 11 mm. When the inferior and superior rectus muscles are concerned, I agree that it is difficult to resect more than 5 or 6 mm. I do not make a recession of the medial rectus muscle of more than 3.5 mm., as I do not like to weaken convergence. When one speaks of the amount of recession, it is important to specify how the sutures are inserted into the muscle. If they are inserted 1 or 2 mm. from the free border, one may be making a recession of 1 or 2 mm. less than was intended. The perforated forceps I use brings the free edge of the muscle in apposition with the sclera, so that 3.5 mm. measures the amount of recession of the muscle.

With respect to recession of the lateral rectus muscle, I am also rather conservative; in cases of heterophoria I may do a recession of about 5.5 mm.; in cases of amblyopia, one of 7 or 8 mm.

In 97 cases of recession of the inferior oblique muscle on which I have accurate preoperative and postoperative data, the screen and parallax test with prisms showed that an average of 1 mm. of recession in the primary position produced 1 $^{\Delta}$ of correction, both at 6 meters and at 25 cm. However, in some cases I found that a recession of the inferior oblique of 5 mm. caused no change in the vertical deviation; in other cases too much correction resulted, but I usually obtained a little less than the average correction.

DR. WALTER W. WRIGHT, Toronto, Canada: No mention was made of the age of the patients. My experience with patients with strabismus has been that my good results were obtained with young children under 4 years of age. With young children much less recession is needed. No child is too young to be operated on if the procedure is indicated.

DR. J. L. MCCOOL, San Francisco: I should like to discuss the technic of the recession which I use. It is a modification of Jamison's and seems to afford a more accurate means of determining the amount of the recession and a somewhat firmer attachment of the muscle stump to its new position.

After the muscle is isolated, the tendon is grasped with the Jamison forceps about 2 or 2.5 mm. from its insertion. The tendon is then cut as close to the sclera as possible, so that some of the fibrous tissue of the insertion is left on the end of the tendon fibers. This has a tendency to hold the tendon fibers together and to act as a buttress when the sutures are placed, binding the tendon to the sclera in its new position.

Three mild chromic double-armed 0000 sutures are then placed in the sclera, in a line parallel to the original insertion. These are then carried through the tendon anterior to the forceps and tied firmly. This method of suturing has two important advantages: a more accurate placement of the sutures in the sclera, and a firmer hold on the tendon, because the suture is tied across the long axes of the fibers and the binding of the fibers at their end helps to prevent any slipping.

The forceps which I show you digs down into what is left of the stump of the tendon and facilitates insertion of the sutures into the sclera by preventing rotation of the globe.

I take exception to Dr. Berens' statement of operating on so many muscles at one time, since the ideal is to preserve, create and educate ultimately the patient in binocular single vision. Many times a shortening of a superior rectus muscle in hyperesotropia will achieve parallelism without any further attack on the lateral rectus muscles.

DR. THOMAS D. ALLEN, Chicago: I want to mention a case on which Dr. James White consulted with me. The patient had a vertical diplopia, which gave him varying amounts of hyperphoria and exophoria in repeated tests and in the cardinal positions. No two of my findings were alike, and yet there was always more or less concomitant hyperphoria. The patient had been injured in a mine four or five months before I saw him. Dr. White stated that he thought the right eye was lower than the left and suggested that a small cartilage graft be placed under the right eye and the eye be raised. This we did. The patient now has normal vision, normal muscular balance, good fusion, no diplopia and almost no hyperphoria or exophoria, and he is extraordinarily happy; and we did not touch a single muscle.

DR. A. DEHART PRANGEN, Rochester, Minn.: In measuring the amount of recession or resection, I think all make about the same estimates but arrive at them in different ways. Perhaps what I call 5 mm. of recession or resection someone else, by his method of measurement, might estimate as more or less. The point I wish to make is that the surgeon makes enough recession or resection to accomplish his objective.

I believe that Dr. Dunnington was the first to advocate the posterior, or global, approach in operating on the inferior oblique muscle.

I was asked how long I keep my patients in bed after surgical procedures in the ocular muscles. I keep them in bed four to six days.

As to the age for muscle surgery, I have long since ceased to regard the age of the patient as of any importance in deciding when to operate or what to do, except that the child should be old enough to undergo a general anesthesia safely. Except for this factor, when the indications for operation are present, I should operate.

Medical Assistance at Professional Level. Dr. Parker Heath, Detroit.

The author discussed the advisability of developing a professional group of ophthalmic associates and stated that such a group could be created within existing educational facilities. The suggested program would run four years at college level and lead to a bachelor's degree. About half the subject matter would lie in the field of the humanities and would be taught by the literary and scientific faculties. The remainder falls largely on the technical side and would be the responsibility of the medical teachers. The standards for admittance would be those of college level plus aptitude. The formation of this group would extend the present medical services and better the lot of the patient.

DISCUSSION

Dr. Conrad Berens, New York: In the training of orthoptic technicians, my colleagues and I have been impressed by the need for this type of service. At first we took any applicant we were able to get; now we almost always insist on a college education as a requirement for admission, for we found that in physiologic optics, for example high school graduates were not able to understand the problems. I hope this idea of Dr. Heath's will receive the approval it merits and that a sufficient number of these technicians will be available soon.

Dr. Heath has pointed out that a sufficient number of ophthalmologists cannot be, and are not, trained. The only realistic approach to the problem of which I know is the Boston plan, which Dr. Lancaster and Dr. Beach are fostering.

Dr. E. C. Ellett, Memphis, Tenn.: Another subject closely related to this problem is the propriety of an ophthalmologist's taking an optometrist into his office for some of this other work which Dr. Heath has discussed, to be done, of course, under supervision.

Dr. William H. Crisp, Denver: The whole subject of the proposed degree and training will have to be coordinated carefully with the question Dr. Ellett has just raised, and also with the development of a special degree in orthoptics. In the long run, movements of this kind have results that one cannot foresee, as in the creation of a new professional class, or new professional classes, which will serve the public in competition with the medical profession. One might also consider the analogy between these movements and what exists in Russia, where there is a special class known as *feldshers,* who are trained in medicine, but on an inferior scale and for a shorter period, and who go out and do certain things in medical practice; and also in Germany, where there are two kinds of dentists, one who is limited as to the kind of work he can do, on a lower level, and another, the dental surgeon, who does the higher

types of work. I merely suggest that the present proposal requires broad consideration and should not lead to hasty action in the establishment of a degree for this purpose.

DR. PARKER HEATH, Detroit: Dr. Berens has long been a pioneer in teaching in this field and has been an inspiration to many who are endeavoring to broaden the scope of the practice of medicine without losing control of it.

We have, in the nursing field, given a special course in ophthalmic nursing, two hours of medical teaching, and the aftermath has been that our patients are better satisfied with certain forms of group nursing; it costs the patients less; they are given better care, and it has almost done away with our need of the special nurse.

In regard to the matter of risks suggested by Dr. Crisp, I believe the same warning was made about nurses and about orthoptic technicians. I think that the hazards and dangers are mostly imaginary, for the group is subject to medical laws and is taught about medicine and medical principles.

The Dissatisfied Refraction Patient. DR. C. A. VEASEY JR., Spokane, Wash.

The author discussed the problems presented to the ophthalmologist by the dissatisfied refraction patient. He reviewed the usual causes of complaint and included some unusual presenting symptoms. Emphasis was placed on the importance of giving the patient the necessary time to voice his complaints and on the necessity of locating the particular trouble and of correcting it or explaining irremediable difficulties.

DISCUSSION

DR. S. JUDD BEACH, Portland, Maine: I should like to emphasize some of the implications of this paper; as Scott Sterling has said, "Overcorrection is the besetting sin of the ophthalmologist." By this, I mean overcorrection not only in presbyopia but also in hyperopia and myopia. The ophthalmologist fools only himself when he imagines he is making his patients emmetropic. Certainly, he tries to find out what will make them emmetropic, but then he modifies that according to the circumstances. I presume it is the experience of every one that most myopic persons do not like to have a complete correction for distance; they usually prefer to wear a correction which will make objects around the room distinct. One reason for what people like to call "shading" a prescription is that every change in lenses produces a different size object and thereby alters the space perception. I have always assumed this to be one reason that it is so easy to give a child, for instance, one with squint, high correction and have it worn with perfect ease, when it is so difficult to give a similar correction to an adult. The adult has been accustomed to associate objects with a certain appearance and size, by which he places them in space, whereas the child has not become so fixed in his ideas. Each patient is an individual, and the prescription and refraction must conform to the patient, and not to the prejudices of the refractionist. The method of refraction should also be adapted to the patient.

Some patients are uncomfortable under fluorescent lighting, and in the office it is reenforced with incadescent desk lights.

Many patients have nothing the matter but a little anemia, or even a low grade fever which comes on in the afternoon, and that is when their eyes are tired.

The ophthalmologist should never forget to write down the visual acuity with the patient's old lenses in order that he may refute the occasional patient's statement that he could see better with his old glasses than he can with the new ones.

Evisceration with Intrascleral Implant: A New Technic. Dr. C. S. O'Brien and Dr. James H. Allen, Iowa City.

The authors described a new technic designed to give a better appearance and better mobility to a prosthesis after evisceration. The method under trial involves the implantation of a "lucite" implant with a peg extending through a trephine opening in the cornea, the evisceration having been done through meridional scleral incision. The prosthesis is then attached to this peg.

DISCUSSION

Dr. William H. Crisp, Denver: I should like to ask whether there has been much tendency to foreign body reaction around the implant, and what is the longest time that any of the patients have worn the implant.

Dr. Wendell L. Hughes, Hempstead, N. Y.: I shall describe here a new type of combined integrated implant and artificial eye. (The commentator then detailed a method of attaching the tendons of the rectus muscles and the fascia directly to a special implant, a removable external prosthesis attachment being then fitted on the implant. The contents of the eye are removed through an incision beneath the superior rectus muscle).

Dr. James H. Allen, Iowa City: I realize that in some cases the scleral implant would be lost and in other cases it would be contraindicated; so I have worked with muscle cone implants. The basic principle of design is that of Col. Norman Cutler, whose implant is a plastic ball in which a gold anterior portion is embedded. The metal part consists of a face with a square hole in it. From the margin of the face four arms extend outward to support a gold ring, to which the four rectus muscles are attached. We have varied the design in several respects, as may be seen in the slides. We use a round hole and have no difficulty with abnormal rotation of the prosthesis.

The muscle cone implant, in addition to the peg principle of Colonel Cutler, includes the groove principle of Wheeler's implant; however, we have added bridges across the grooves, a device which traps the rectus muscles and prevents the implant from slipping. The technic following enucleation consists in slipping the rectus muscles through the grooves and under the bridges. The ends of the muscles are split and the lateral and medial rectus muscles are overlapped and sutured together around the peg. The conjunctiva and Tenon's capsule are closed with a purse string suture, which pulls them down around the peg.

If the intrascleral implant fails, it is still possible to insert a muscle cone implant, as demonstrated in the accompanying moving picture. One of the advantages of direct contact between the implant and the prosthesis, as emphasized by Colonel Cutler, is rapid immediate movement of the prosthesis, even over small ranges.

DR. C. S. O'BRIEN, Iowa City: This operation is still on trial. We have had no trouble with corneal sensitivity. We lost several implants because in the first operation we excised the cornea and sutured the sclera around the peg. In the next operations the incision was grooved, and even then it pulled loose; but with the present meridional incision we believe that we have found the correct technic, although the one advocated by Dr. Hughes may be the answer.

Tenotomy of the Superior Oblique Muscle for Hypertropia.
DR. RAYNOLD N. BERKE, Hackensack, N. J.

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DISCUSSION

DR. FREDERICK C. CORDES, San Francisco: Overaction of the superior oblique muscle is rare in our experience. When it does occur, it is the result of one of a number of conditions: (1) paresis of the inferior rectus muscle of the opposite side, (2) paresis of the homolateral inferior oblique muscle or (3) primary overaction of the superior oblique muscle. The last is probably rare, as the inferior oblique, being inserted higher and being a stronger muscle, has anatomic advantages.

The commonest cause of overaction of the superior oblique muscle is paresis of the contralateral inferior rectus muscle, and the treatment usually advocated is weakening the yoke muscle if the paretic eye is used for fixation. If the nonparetic eye is used for fixation, the paretic muscle should be strengthened and the antagonist weakened if spasm has developed. Most ophthalmologists are in accord with Sanford Gifford's statement that it is "inadvisable to disturb the opposite superior oblique."

Dr. Berke's operation seems safe, simple and logical, but one wonders whether the percentage of cases of complete loss of function will be so high that the operation will have to swing over to recession of the muscle at its insertion, as had to be done in the case of the medial and rectus inferior oblique muscles.

The importance of a correct diagnosis cannot be stressed too much. Overaction of the superior oblique is the description of a condition, and the diagnosis of the cause is of great importance in making the decision as to the procedure indicated. High lateral deviation had better be corrected before operation on the vertical muscles is attempted. In high degrees of deviation some of the vertical muscles are in the field of least action. For example, in high exotropia, owing to the oblique muscles being in the field of least action, one may obtain a faulty conception of their action unless these muscles are studied after the lateral deviation has been corrected.

My experience with the operation is limited to 1 case, and I had no difficulty in carrying out Dr. Berke's technic. The importance of not freeing the fine lateral fibrillae that pass from the tendon to the sheath bears emphasis.

DR. WENDELL L. HUGHES, Hempstead, N. Y.: Operations on the superior oblique muscle have been avoided by ophthalmologists for two reasons: difficulty of technic and difficulty of diagnosis. Abnormal action of the depressors of the eye are often difficult to determine.

Wheeler described an operation for increasing the action of the superior oblique by tucking the tendon, and in 1944 I presented the

operation of recession of the trochlea for reducting the action of the superior oblique (*Am. J. Ophth.* **27**:1123 [Oct.] 1944). However, Dr. Berke's operation is superior, for several reasons:

It affords (1) greater ease of technic and (2) greater certainty of results, because of better exposure, and (3) the amount of weakening effect can be at least partially controlled.

I have performed the operation twice in the past month; in 1 case too much effect was obtained, and in the other a satisfactory result was obtained. If the tendon is severed too near the trochlea, the cut end may be retracted to or through the trochlea.

A comparison may be made with tenectomy of the inferior oblique muscle. In myectomy of the inferior oblique, if the capsule is removed with the piece of muscle, one may readily obtain complete paralysis; but if the muscle is carefully dissected from its capsule and only the muscle fiber is removed, one will not get complete paralysis. The muscle remains attached to its original position by means of the capsule.

I am of the opinion that the operation described is indicated in all cases in which there is any overaction of the superior oblique muscle, with or without reduced action of the associated inferior rectus of the opposite eye.

DR. RAYNOLD N. BERKE, Hackensack, N. J.: The first patient operated on eight years ago shows no signs of paralysis of the superior oblique. Overaction of the superior oblique is due, as Dr. Cordes stated, to weakness of the contralateral inferior rectus or to weakness of the homolateral inferior oblique; but, as Dr. Hughes pointed out, sometimes it is impossible to state which of these muscles is primarily at fault. Fortunately, in such cases tenotomy of the superior oblique is just as effective as in cases in which one is able to make a positive diagnosis. Over one-half our patients had an exotropia which was greater in the lower fields. This was attributed to the divergent power of the superior oblique muscles. The last patient whose case I presented had a hypertropia with an exotropia before operation. In this case both the lateral and the vertical deviation were corrected by bilateral tenotomy of the superior oblique muscle.

Combined Red Filter and Occluder with Several Uses. DR. WENDELL L. HUGHES, Hempstead, N. Y.

The author described an instrument consisting of a ground plastic red filter, blackened on one end with a handle in the middle and used with a green light at 20 feet (6 meters) for fixation. A quick method of determining the balance of the extraocular muscles, using the instrument and the proper prisms in the parallax test, was described. The instrument may be employed also as an occluder as well as for performing the alternate cover test and for checking gross fusion.

Instrument for Use in the Recession Operation for Squint. DR. ANGUS L. MACLEAN, Baltimore.

To avoid vertical heterophoria after a recession, an instrument was devised to facilitate the placing of the end of the recessed muscle in correct alinement with the original insertion.